EFECTO DE UNA DIETA SALUDABLE SOBRE EL PERFIL LIPÍDICO, GLICEMIA, INSULINEMIA, EXPRESIÓN DE GENES PROINFLAMATORIOS Y DE ESTRÉS OXIDATIVO EN ADULTOS CON OBESIDAD ORIUNDOS DE LA REGION CAFETERA COLOMBIANA.

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Tesis de Doctorado presentada como requisito parcial para optar al título de Doctora en Ciencias Biomédicas

Universidad de Caldas
Manizales
2023

NOTA DE ACEPTACIÓN

Los abajo firmantes, convocados por el programa de Doctorado en Ciencias Biomédicas de la Universidad de Caldas hemos revisado el informe final de la tesis doctoral:

EFECTO DE UNA DIETA SALUDABLE SOBRE EL PERFIL LIPÍDICO, GLICEMIA, INSULINEMIA, EXPRESIÓN DE GENES PROINFLAMATORIOS Y DE ESTRÉS OXIDATIVO EN ADULTOS CON OBESIDAD ORIUNDOS DE LA REGION CAFETERA COLOMBIANA.

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Fecha de sustentación 21/09/2023

A mis hijos por valorarme como lo hacen.

A mis seres más amados que no tuvieron la oportunidad de verme culminar este proceso:

Mi mamá y mi hermano por su apoyo incondicional no solo en este arduo proceso de formación académica, sino en cualquier otro proyecto que emprendí.

Mi compañero de vida quien siempre me animó y motivó a continuar.

AGRADECIMIENTOS

A la doctora Clara Helena González Correa, mi directora, por su calidad humana, su optimismo y siempre buena energía, por su amplitud con el conocimiento, su capacidad para guiar el proceso de formación doctoral de lo simple a lo complejo; desde la concepción del proyecto, su escritura, consecución de recursos, ejecución hasta la publicación de los resultados. Igualmente, a mi codirectora, la doctora Maria Magdalena Echeverry de Polanco por su confianza.

A los doctores, Oriol Rangel Zúñiga y Dr. Antonio Camargo investigadores del grupo G09 Nutrigenómica y Síndrome metabólico del Maimónides, de Investigación Biomédica de Córdoba (IMIBIC) en España, por recibirme con los brazos abiertos en su grupo, darme toda la facilidad y poner a disposición sus conocimientos y todo su equipo de trabajo para realizar los ensayos necesarios para la culminación de este proyecto.

A la doctora, Gloria Liliana Porras, de la Clínica Comfamiliar Pereira por creer en este proyecto y facilitar los espacios: laboratorio, sala de toma de muestras y lo más importante: los pacientes a través de la base de datos del programa de enfermedades crónicas de la Clínica Comfamiliar.

A los profesores del Doctorado en Ciencias Biomédicas por loa aportes recibidos en cada seminario.

Al Departamento Administrativo de Ciencia, Tecnología e Innovación (COLCIENCIAS), por el apoyo económico mediante el Programa Nacional para la Formación de Investigadores y Convocatoria de Doctorados Nacionales No. 647 de 2015.

A la Vicerrectoría de Investigaciones y Posgrados de la Universidad de Caldas por la financiación y ejecución de parte de los recursos del proyecto

A la Direccion Seccional de Investigaciones de la Universidad Libre Pereira por el apoyo económico a uno de los objetivos del proyecto.

A Industrias Kallu por la donación de su chocolate amargo.

A mis Compañeros del doctorado Marcela, Paula, Amilbia y Juan Carlos por sus voces de aliento en todo el proceso.

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ABREVIATURAS Y DEFINICIONES

ADN: Ácido desoxirribonucleico
ATP: Adenosin trifosfato
CMSP: Células mononucleares de sangre periférica
DHA: Ácido docosahexaenóico
DM: Dieta Mediterránea
DMT2: Diabetes Mellitus tipo 2
ECNT: Enfermedades crónicas no transmisibles
ECV: Enfermedad cardiovascular
EDTA: Ácido etilamino-tetracético
ENSIN: Encuesta nacional de situación nutricional
EPA: Ácido eicosapentaenoico
FAWGT: Frutas aguacate granos enteros trucha, por sus siglas en ingles
FDA: US Food and Drug Administration
GLP1: Péptido 1 similar al glucagón
HDL: Lipoproteínas de alta densidad
IKB: Proteína IKB
IL: Interleuquina
IL1β: Interleuquina 1 Beta
IL6: Interleuquina 6
IL18: Interleuquina 18
IMC: Índice de masa corporal
LDL: Lipoproteínas de baja densidad
LPS: Lipopolisacáridos
MUFA: Ácidos grasos monoinsaturados
NF-κB: Factor de transcripción nuclear Kappa B
OMS: Organización mundial de la salud
PAI: Inhibidor activador del plasminógeno
PCR: Proteina C reactiva
PUFA n-3: ácidos grasos poliinsaturados n-3 de cadena larga y de origen marino
RNA: Ácido ribonucléico
ROS: Especies de oxigeno reactivo
SFA: Ácidos grasos saturados
TG: Triglicéridos

TNFα: Factor de necrosis tumoral alfa

UD: Dieta usual, por sus siglas en ingles

VLDL: Lipoproteínas de muy baja densidad

VCT: Valor calórico total

WAT: Tejido adiposo blanco, por sus siglas en ingles.

RESUMEN

La obesidad es una enfermedad crónica, causada por un desequilibrio entre la ingesta y el gasto energético, con una subsecuente acumulación de grasa que puede ser perjudicial para la salud.

En el 2016 se reportaron a nivel mundial, más de 1.250 millones de personas mayores de 18 años con sobrepeso y más de 650 millones eran obesas, este problema de salud pública, es un factor de riesgo importante para el desarrollo de enfermedades crónicas no transmisibles. El vínculo entre la obesidad y estas enfermedades es una inflamación crónica de bajo grado, que puede detectarse a través de la expresión de genes proinflamatorios y de estrés oxidativo o, por alteraciones de vías metabólicas como la de señalización de insulina, homeostasis de glucosa, metabolismo lipídico y microbiota intestinal. Los cambios asociados a la obesidad pueden ser inducidos por un patrón de dieta occidental alta en grasas saturadas, azucares y alimentos procesados, por el contrario, una dieta basada en grasas saludables, granos enteros, alto contenido de frutas y verduras puede prevenirlos o disminuirlos. **Objetivo:** Evaluar en adultos obesos, el efecto de una dieta rica en frutas, verduras, granos enteros, aguacate y trucha sobre marcadores de inflamcion crónica de bajo grado como: el perfil lipídico, glicemia, insulinemia, expresión de genes proinflamatorios, de estrés oxidativo y microbiota intestinal, con el fin de mejorarlos. **Metodología:** 1. Revisión sistemática exploratoria, del efecto de distintas dietas sobre marcadores de inflamación identificando los mas evaluados. 2. Estudio preliminar paralelo, aleatorizado controlado y exploratorio para determinar el efecto postprandial de dos comidas; a 64 jóvenes sanos, del eje cafetero. 3. Para la evaluación del efecto de la dieta cafetera sobre el perfil lipídico, la glicemia y la insulinemia, además de la expresión génica, se incluyeron 44 adultos (34 mujeres y 10 hombres), con un índice de masa corporal igual o mayor 30 Kg/m^2. A través de un diseño cruzado aleatorizado los participantes fueron sometidos a dos dietas, de 8 semanas cada una: la primera dieta – FAWGT-, por sus siglas en ingles, fue suplementada con frutas y verduras, aguacate, granos enteros y trucha; la segunda correspondio a la dieta usual de los participantes -UD-, por sus siglan en ingles, caracterizada por el consumo de grasas saturadas y carbohidratos procesados; se tomaron muestras en ayuno y en estado postprandial (4 horas) antes y después de cada intervención. 4. Para el análisis del efecto de la dieta sobre la microbiota intestinal, se realizó un estudio paralelo, controlado y aleatorizado con una submuestra de 29 mujeres, sometidas a una de las dos dietas durante 8 semanas (FAWGT n=17 y UD n=12).

Se obtuvieron muestras de materia fecal antes y después de cada intervención.

Todos los participantes firmaron un consentimiento informado; el protocolo de investigación fue aprobado por el Comité de Ética de la Universidad de Caldas y de la Clínica Comfamiliar y registrado en Clinical Trials.gov (NTC04920409). **Resultados: 1.** La revisión sistemática que incluyó 14 estudios con 1470 participantes arrojó que dietas ricas en ácidos grasos poliinsaturados reducen los niveles de proteína C reactiva y el consumo de una Dieta Mediterránea, enriquecida con aceite de oliva y nueces disminuye los niveles séricos de interleuquina 6 y de moléculas de adhesión endotelial, sin cambios en el factor de necrosis tumoral α. 2. El consumo de una comida rica en carbohidratos complejos y baja en grasa no disminuyó la lipemia postprandial comparada con una comida rica en grasa y baja en carbohidratos. Los resultados obtenidos permitieron realizar ajustes para el estudio con participantes obesos 3. Después del consumo de la dieta FAWGT se encontró, en estado postprandial, un menor incremento de los niveles de insulina y triglicéridos y de la expresión de genes proinflamatorios (*IL-6, IL 1B, NFKB1*) y del gen *NEF2L2* relacionado con estrés oxidativo. 4. Con la dieta FAWGT disminuyó la abundancia relativa de la familia Veillonellaceae y con la dieta usual disminuyó la abundancia relativa del genero Roseburia. **Conclusiones:** El consumo de una dieta suplementada con frutas, verduras, aguacate, granos enteros y trucha, mejora la microbiota intestinal y el proceso inflamatorio y de estrés oxidativo que se produce en estado postprandial, en adultos con obesidad y podría ser considerada una alternativa a otras dietas cardiosaludables.

Palabras clave

Obesidad, dieta, inflamación, estrés oxidativo, insulinemia, glicemia, perfil lipídico, expresión génica, microbiota intestinal

ABSTRACT

Obesity is a chronic disease caused by an imbalance between energy intake and expenditure, with a subsequent accumulation of fat that can be detrimental to health. In 2016 it was reported worldwide, more than 1.25 billion people over the age of 18 were overweight and more than 650 million were obese, this public health problem, is a major risk factor for the development of chronic non-communicable diseases. The link between obesity and these diseases is chronic low-grade inflammation, which can be detected through the expression of proinflammatory and oxidative stress genes or by alterations in metabolic pathways such as insulin signaling, glucose homeostasis, lipid metabolism and intestinal microbiota. The changes associated with obesity can be induced by a Western dietary pattern high in saturated fats, sugars and processed foods, on the contrary, a diet based on healthy fats, whole grains, high content of fruits and vegetables can prevent or decrease them. **Objective:** To evaluate in obese adults, the effect of a diet rich in fruits, vegetables, whole grains, avocado and trout on markers of low-grade chronic inflammation such as: lipid profile, glycemia, insulinemia, expression of proinflammatory genes, oxidative stress and intestinal microbiota in order to improve them. **Methodology:** 1. Exploratory systematic review of the effect of different diets on inflammation markers identifying the most evaluated ones. 2. Preliminary parallel, randomized controlled and exploratory study to determine the postprandial effect (4 hours) of two meals; 64 healthy young people, from the coffee-growing area. 3. For the evaluation of the effect of the coffee diet on the lipid profile, glycemia and insulinemia, in addition to gene expression, 44 adults (34 women and 10 men) with a body mass index equal to or greater than 30 kg/m2 were included. Through a randomized crossover design, the participants were submitted to two diets of 8 weeks each: the first diet - FAWGT - was supplemented with fruits and vegetables, avocado, whole grains and trout; the second corresponded to the usual diet of the participants -UD-, characterized by the consumption of saturated fats and processed carbohydrates; fasting and postprandial samples were taken before and after each intervention. 4. For the analysis of the effect of the diet on the intestinal microbiota, a parallel, controlled, and randomized study was carried out with a subsample of 29 women, subjected to one of the two diets for 8 weeks (FAWGT n=17 and UD n=12). Stool samples were obtained before and after each intervention.

All participants signed an informed consent; the research protocol was approved by the Ethics Committee of the University of Caldas and the Comfamiliar Clinic and registered in Clinical Trials.gov (NTC 04920409).

Results: 1. The systematic review that included 14 studies with 1470 participants showed that: 1.1 Diets rich in polyunsaturated fatty acids reduce the levels of C-reactive protein. 1.2 The consumption of a Mediterranean diet, enriched with olive oil and walnuts decreases serum levels of interleukin 6 and endothelial adhesion molecules, without changes in tumor necrosis factor α. 2. The consumption of a meal rich in complex carbohydrates and low in fat did not decrease postprandial lipemia compared with a meal rich in fat and low in carbohydrates. The results obtained allowed adjustments to be made for the study with obese participants. 3. After consumption of the FAWGT diet, a decrease in insulin and triglyceride concentrations and in the expression of proinflammatory genes (*IL-6, IL 1B, NFKB1)* and of the *NEF2L2* gene related to oxidative stress. 4. The FAWGT diet decreased the relative abundance of the Veillonellaceae family, and the usual diet decreased the relative abundance of Roseburia genus. **Conclusions:** The consumption of a diet supplemented with fruits, vegetables, avocado, whole grains, and trout, improves the intestinal microbiota and the inflammatory process and oxidative stress that occurs in postprandial state, in adults with obesity and could be considered an alternative to other heart-healthy diets.

Key words.

Obesity, diet, inflammation, oxidative stress, insulinemia, glycemia, lipid profile, gene expression, gut microbiota.

INTRODUCCIÓN

Planteamiento del problema

La obesidad es causada por un desequilibrio entre la ingesta y el gasto energético, con una subsecuente acumulación de grasa que puede ser perjudicial para la salud. En el 2016 más de 1.900 millones de personas mayores de 18 años tenían sobrepeso y, de ellos, más de 650 millones eran obesos (1). Esta cifra se ha incrementado en las últimas décadas, tanto en países desarrollados como en vía de desarrollo, pasando de 108 millones en 1982 a 422 millones en 2014 (2). Si esta tendencia se mantiene para el 2030 más del 57,8% (3.3 billones de personas) de la población mundial adulta tendrá sobrepeso u obesidad (3). En Colombia, la frecuencia de la obesidad ha aumentado en comparación con otros problemas como la desnutrición y las enfermedades infecciosas (4). La encuesta nacional de situación nutricional (ENSIN) del año 2015, mostró un aumento de 5 puntos porcentuales, en la población de 18 años o más, entre los años de 2005 y 2015 (13,7 a 18,7 % respectivamente) (5).

Por ser uno de los factores de riesgo más importantes para el desarrollo de enfermedades crónicas no transmisibles (ECNT), la obesidad constituye un problema de salud publica, por su asociación con algunas de ellas, a saber: diabetes tipo 2, hipertensión y dislipidemia entre otras, que en su conjunto son responsables del 70% de las muertes en el mundo (6,7), aumentando los gastos de tratamiento y menoscabando el bienestar ,individual y familiar de la población (8).

El vínculo entre la obesidad y las ECNT es un inflamación crónica de bajo grado (9,10). En el año 1993 Hostamisligil et al (11) determinaron la existencia de esta relación, demostrando que la citoquina proinflamatoria factor de necrosis tumoral alfa (TNFα), era expresada en tejido adiposo de ratones obesos y este hecho estaba vinculado con la resistencia a la insulina (12–14). La inflamación crónica de bajo grado, altera una serie de vías metabólicas, como la via de señalización de la insulina, la homeostasis de la glucosa y el metabolismo de los lípidos (9). En sujetos con obesidad se produce un remodelamiento del tejido adiposo, tanto a nivel estructural como funcional, lo que ocasiona hypoxia y la activación de distintas respuestas celulares como inflamación y estrés oxidativo (12). A nivel inflamatorio, hay infiltración de macrófagos y células T estimulando la producción de citoquinas proinflamatorias (IL6, IL1β, IL8), moléculas inflamatorias como TNFα y el inhibidor activador de plasminógeno (PAI), entre otras.

Además, el adipocito va perdiendo su capacidad para almacenar ácidos grasos aumentando su liberación, lo que conduce a una acumulación de estos en otros órganos como el páncreas, el higado y el endotelio contribuyendo al desarrollo de la resistencia a la insulina y a una desregulación en la secreción de leptina y de adiponectina (9).

El estrés oxidativo se manifiesta con un aumento de las especies reactivas de oxigeno (ROS), producto de un desequilibrio entre los sistemas que las producen y los sistemas que las eliminan. Además de producir daño a distintas estructuras celulares, también está asociado a procesos de envejecimiento y de inflamación (15).

Estos procesos inflamatorios se caracterizan por la activación del factor de transcripción nuclear Kappa β (NF-kβ), tanto en adipocitos como en macrófagos. Este factor está formado por dos subunidades (p65 y p50), unidas a IKB, que es la molécula que lo mantiene inactivo en el citoplasma. Su activación permite la escisión de IKB y posterior traslocación al núcleo para iniciar la transcripción de genes diana que median la proliferación celular y citocinas que activan la respuesta inmune (16). La activación de NF-κB está mediada por receptores Toll que juegan un papel fundamental en la activación o supresión de genes relacionados con la inflamación (10).

Otro factor que contribuye a la inflamación de bajo grado, es el desequilibrio en la composición de la microbiota intestinal presente en la obesidad, mostrando una menor abundancia y riqueza (17,18). Esta disbiosis aumenta la permeabilidad intestinal, permitiendo el paso de lipopolisacárido (LPS) al torrente sanguíneo, lo que podría contribuir a la patogénesis de la obesidad y la Diabetes Mellitus tipo 2 (DMT2), a través de la activación de la vía de señalización de NF-kB (19). **Figura 1.**

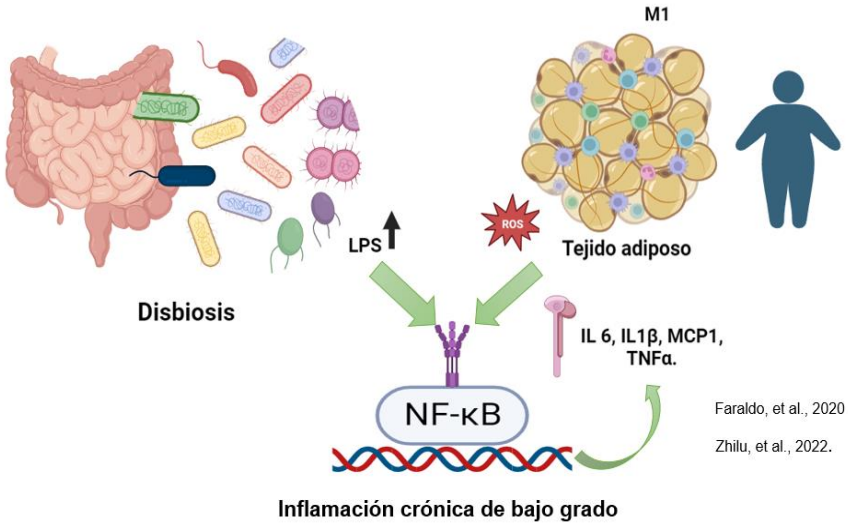

Figura1. Esquema representativo de la inflamación crónica de bajo grado en la obesidad. LPS: lipopolisacárido; M1: macrófagos tipo M1; IL1β: Interleuquina 1β; IL6: Interleuquina 6; TNFα: factor de necrosis tumoral alfa; MCP1: proteína monocito quimioatrayente 1; NF-kB: factor de transcripción nuclear NF-κB.

Con base en lo que se ha venido mostrando, puede afirmarse que la obesidad es el resultado de una compleja interacción entre factores genéticos, metabólicos y factores ambientales incluyendo los hábitos alimentarios (20); en las sociedades occidentales, los hábitos alimentarios han sufrido cambios influenciados por la disponibilidad de productos ultra procesados, hipercalóricos, económicos y de fácil preparación (21). Este patrón alimentario se caracteriza por ser rico en grasas saturadas, azúcar y granos refinados, lo que se ha asociado a un aumento en la tasa de ECNT (22). Algunos estudios muestran como este modelo dietario incrementa la activación del factor de transcripción nuclear Kappa B (NF-KB y la expresión de citoquinas proinflamatorias (23).

La Organización Mundial de la Salud (OMS) ha recomendado efectuar cambios en los patrones alimentarios que incluyen: equilibrar la ingesta de energía, limitar las grasas saturadas y las trans, cambiando hacia el consumo de grasas no saturadas, aumentando la ingesta de frutas y verduras, y limitando la ingesta de azúcar y sal (24). Estos cambios, considerados saludables, pueden disminuir la inflamación crónica y mejorar el metabolismo de lípidos y glucosa, previniendo el riesgo de desarrollar ECNT (25).

Una revisión que incluyó 17 estudios y 2300 sujetos, mostró que un patrón dietario saludable como la dieta mediterránea (DM) disminuye marcadores de inflamación como la proteína C reactiva (PCR) y la Interleucina 6 (IL6) (26).

Igualmente, Leder y colaboradores encontraron que una dieta nórdica saludable podía modular los niveles de RNA mensajero de los genes *TLR4, IL18, CD36,* y *PPARD* en comparación con una dieta control (27).

Los patrones dietarios que incluyen alimentos ricos en omega 3, fibra y antioxidantes disminuyen el estrés oxidativo y los procesos inflamatorios en ayuno y en estado postprandial, que es el estado en el que permanecemos los seres humanos la mayor parte del tiempo, en la sociedad actual (28–30).

Dieta y estado postprandial

La ingesta de tres o más veces al día, ocasiona que el ser humano permanezca en estado postprandial la mayor parte del día (31). En este estado el cuerpo humano está expuesto a una mezcla de macronutrientes, señales endocrinas, factores derivados del intestino y otros, con diferentes picos plasmáticos, por lo que es un estado dinámico, complejo en donde casi todos los órganos y tejidos están implicados.

De hecho, los diferentes factores que componen gran parte de la respuesta postprandial influyen posteriormente en el metabolismo, la inflamación y la salud (32).

La ingesta de una dieta alta en grasas y/o alta en carbohidratos, ocasiona una respuesta inflamatoria postprandial caracterizada por un aumento exagerado de la glucosa sanguínea y un aumento de las lipoproteínas ricas en triglicéridos (VLDL), quilomicrones y sus remanentes. Además, involucra distintas hormonas como se muestra en la **Figura 2.**

El estado postprandial genera un incremento del estrés oxidativo y un aumento transitorio de moléculas pro-inflamatorias liberadas por leucocitos y células endoteliales. En circunstancias saludables parece ser una respuesta protectora para contrarrestar los posibles efectos nocivos de los macronutrientes. Sin embargo, estar en este estado durante más de 16 horas al día puede dar lugar a que el sistema inmunitario permanezca activo continuamente, lo que desencadena una inflamación crónica de bajo grado, favoreciendo el desarrollo de ECNT (33).

La ingesta de una comida genera una respuesta metabólica aguda que incluye una rápida remodelación de las lipoproteínas en comparación con el estado de ayuno en el que estas lipoproteínas se mantienen estables. Igualmente, incluye un aumento de los niveles de triglicéridos dentro de la primera hora y pueden mantenerse elevados de 5 a 8 horas (34) . La capacidad para regular los niveles de triglicéridos despues de la ingesta, determinan la eficiencia metabolica de los individuos.

Por el contrario, un retraso en el retorno a los niveles normales, representa una respuesta alterada a la ingesta de alimentos que podría reflejar la existencia de insulinorresistencia (35)

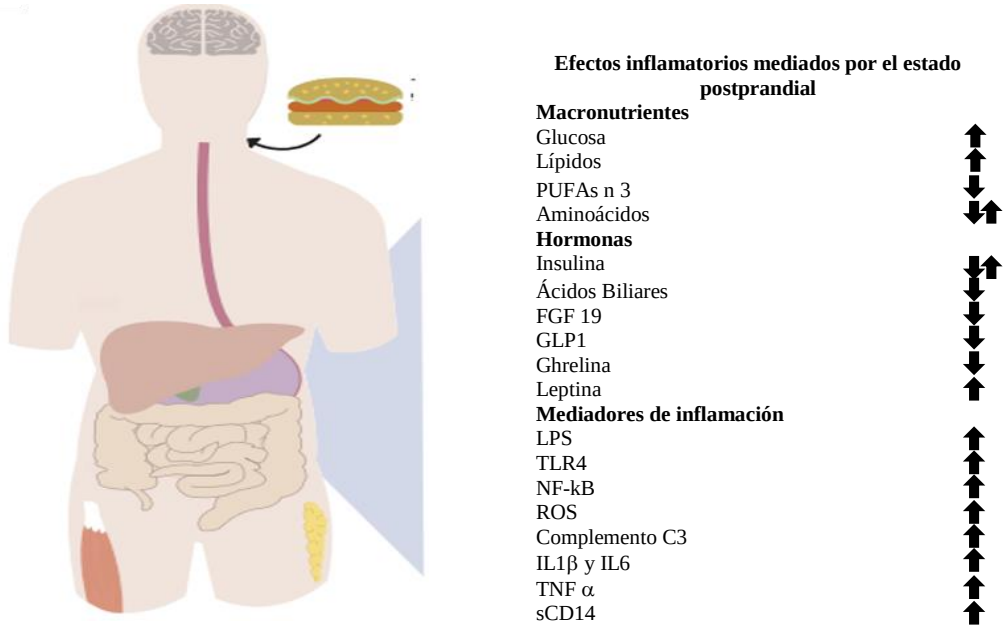

Figura 2. Síntesis del periodo postprandial. Adaptado de Meessen 2019 (36). PUFAs n 3: ácidos grasos poliinsaturados omega 3; FGF 19: factor de crecimiento de fibroblasto 19; GLP1: péptido similar al glucagón tipo 1; LPS: lipopolisacárido; TLR4: receptor Toll 4; NF-kB: factor de transcripción nuclear Kappa B; ROS: especies reactivas de oxígeno; C3: componente 3 del complemento; IL-1β y IL-6 Interleuquinas 1B y 6; TNFα: factor de necrosis tumoral alfa; sCD14: CD14 soluble.

Justificación

La obesidad es una enfermedad multifactorial, en donde están involucrados tanto factores genéticos como ambientales. Dentro de los factores ambientales, la dieta es un factor fundamental en el desarrollo y prevención de la enfermedad. Un estudio en Estados Unidos evaluó 17 factores de riesgo y encontró que la composición de la dieta constituía el grupo más grande de factores de riesgo, responsables de muerte en ese país (26%) (37). El hecho de ser un factor modificable, haceque hace que las intervenciones dietarías sean de gran utilidad para el tratamiento y prevención de ECNT.

El consumo de dietas saludables como la Mediterránea o la Nórdica se ha asociado con beneficios para la salud (38). Sin embargo, los alimentos que componen estas dietas no son de fácil adquisición en regiones diferentes a aquellas donde se consumen habitualmente. Colombia por su diversidad geográfica, climática y biológica, conforma diferentes ecosistemas, que interactúan con la riqueza cultural y la ubicación ecuatorial entre otros factores, le permiten producir gran variedad de especies vegetales durante todo el año y dispone de una diversidad de productos en el mercado interno.

Según la corporación Colombia Internacional, en el año 2012 se ofrecían 42 tipos de frutas y 30 verduras diferentes en los mercados locales (39) . A pesar de estas ventajas, el perfil nacional del consumo de frutas y verduras del año 2015, evidencio que la población colombiana consume en promedio de 0,4 y 0,8 porciones/día respectivamente (40) , muy por debajo de la recomendación establecida por la OMS de 5 porciones/día (1). Teniendo en cuenta lo expuesto anteriormente, esta investigación estableció, como desenlace principal, la disminución de la inflamación crónica de bajo grado y el estrés oxidativo que se produce en estado postprandial, después de una ingesta aguda y 8 semanas después de una intervención con una dieta diseñada con alimentos disponibles en la región cafetera colombiana (frutas, verduras, granos enteros, aguacate y trucha) (41,42). Se enfocó en una dieta mixta -no en un ùnico componente-, ee decir una mezcla de alimentos que interactúan entre ellos y potencian su efecto sobre la salud (43).

Los resultados de este estudio podrían ser un insumo para el desarrollo de políticas públicas encaminadas a la prevención de la obesidad y sus comorbilidades.

Tendencias bibliométricas

Se realizó un análisis de las tendencias bibliométricas a partir de la base de datos *Scopus* teniendo en cuenta tres aspectos: relación y coocurrencia entre palabras claves, evolución de las palabras clave desde el año 2018 al 2022 y las revistas más populares para difusión de información del tema relacionado en los últimos años. Como se muestra en la Figura 3a, la obesidad está estrechamente relacionada con la inflamación y la microbiota y estas a su vez con la dieta y algunos géneros bacterianos; las palabras claves más utilizadas por la comunidad científica para el 2022 en relación al tema son: "*gut microbiota*, *obesity*, *inflammation*, *lipid metabolism*, *intestinal permeability*, *disbiosis* y *fat accumulation"*. A pesar de tener una ventana de tiempo relativamente corta (3 años) la prevalencia de las palabras clave ha cambiado.

La figura 3b muestra que en 2018 las investigaciones estaban dirigidas hacia el síndrome metabólico y enfermedades como la diabetes, para el 2022 aumentaron las publicaciones relacionadas con la microbiota intestinal, obesidad e inflamación. Por último, la figura 3c resalta la revista "*Nutrients*" de la editorial MDPI como la principal fuente de divulgación de las investigaciones relacionadas con el tema que se está desarrollando. De acuerdo con este análisis bibliométrico, nuestro estudio es concordante con las tendencias encontradas a nivel mundial y útil e innovador para nuestra zona geográfica de interés.

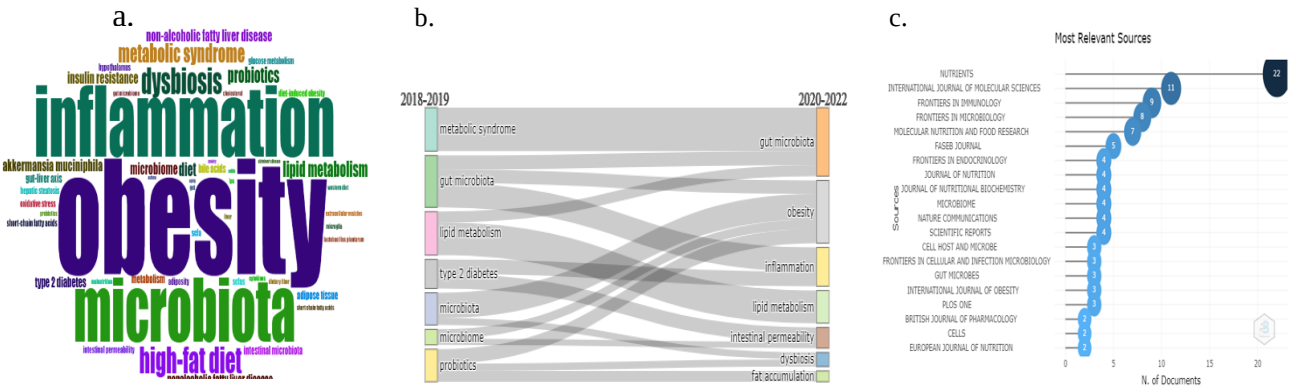

Figura 3. Tendencias bibliométricas relacionadas a los tópicos "*obesity*" AND "*microbiota*" AND "*inflammation*" para un intervalo de tiempo de 2018 a 2022 en la base de datos *Scopus*. **A.** nube de palabras realizada con la coocurrencia de palabras clave. **B.** Evolución de las palabras en dos puntos de corte 2018 y 2022 a partir de las palabras clave. **C.** Diagrama de frecuencia de las revistas más relevantes en el tema. Graficas generadas con el paquete Bibliometrix usando el ambiente de R y la versión R Studio in Windows 10 versión 1.442.

HIPÓTESIS

Observación: En Colombia y en particular en la región cafetera existe una tendencia hacia dietas poco saludables, este es uno de los aspectos que ha contribuido al aumento de la obesidad.

Hipótesis: El consumo durante ocho semanas, de una dieta rica en frutas, verduras, granos enteros (arepa y arroz integral); aguacate y trucha, alimentos disponibles en la región, disminuye la expresión de genes proinflamatorios y de estrés oxidativo en células mononucleares de sangre periférica, mejora los marcadores metabólicos y de inflamación en plasma y modifica la microbiota intestinal en adultos con obesidad.

OBJETIVOS

Objetivo General

Evaluar en adultos obesos, el efecto de una dieta suplementada con frutas, verduras, granos enteros, aguacate y trucha sobre marcadores de inflamación crónica de bajo grado como: perfil lipídico, glicemia, insulinemia, expresión de genes proinflamatorios, estrés oxidativo y microbiota intestinal con el fin de mejorarlos.

Objetivos Específicos

1. Identificar el efecto de dietas saludables sobre marcadores de inflamación a través de una revisión sistemática, utilizando como fuente las bases de datos: PubMed, Scopus y Science direct, con el fin de construie la matriz bibliográfica de referencia para el estudio.

2. Evaluar el efecto agudo del consumo de dos desayunos sobre la lipemia postprandial en adultos jóvenes.

3. Verificar el impacto de dos dietas (FAWGT y UD), en adultos con obesidad, comparando marcadores como: glicemia, lípidos e inflamación, obtenidos antes y después de 8 semanas, en estado de ayuno y postprandial, con el fin de socializar con los terapeutas como parte del tratamiento y la prevención de la obesidad de la obesidad y demás ECNT asociadas.

4. Evaluar el efecto de la dieta FAWGT, sobre la expresión de los genes *NFKB1, RELA, MMP9, TNF, IL1B, IL6, IKKA* y el gen *NFE2L2* involucrados en procesos inflamatorios y de estrés oxidativo, analizándolos en personas adultas con obesidad, con el fin de que la dieta sea tenida en cuenta en el tratamiento y la prevención.

5. Determinar el efecto de la dieta FAWGT, sobre la microbiota intestinal en mujeres adultas con obesidad, con el fin de establecer la relación con marcadores de inflamación crónica de bajo gardo.

ESQUEMA DE LA TESIS

Capítulo I: artículo de revisión sistemática titulado **"Effect of Dietary Intervention on Inflammatory and Endothelial Dysfunction Markers in Adults with Metabolic Syndrome: A Systematic Review"** que establece la relación entre distintos patrones dietarios y la inflamación crónica de bajo grado a través de la evaluación del cambio en las concentraciones de TNF α, IL 6, proteína C reactiva (PCR), después de una intervención dietaría.

Capítulo II: artículo de investigación: **"Postprandial lipid profile in young colombian people. A comparison of two breakfasts"** en el cual se evaluó el efecto agudo de dos desayunos isocalóricos sobre la lipemia postprandial, que fue un insumo para el desarrollo del segundo objetivo de la tesis.

Capítulo III: artículo titulado: **"Alternative Foods in Cardio-Healthy Dietary Models That Improve Postprandial Lipemia and Insulinemia in Obese People"** que aborda el tercer objetivo de la tesis.

Capítulo IV: artículo denominado **"Effect of 8 weeks of consumption of a dietary pattern based on fruits, avocado, whole grains and trout on postprandial inflammatory and oxidative stress gene-expression in obese people"**, producto del objetivo 4 de esta tesis.

Capitulo V: articulo denominado "

Capitulo VI: **discusion general.**

Capitulo VII: **conclusiones y recomendaciones.**

Adicionalmente, se detallan las actividades complementarias realizadas durante la formación doctoral.

CAPITULO I: Effect of Dietary Intervention on Inflammatory and Endothelial Dysfunction Markers in Adults with Metabolic Syndrome: A Systematic Review

Capítulo I: Effect of Dietary Intervention on Inflammatory and Endothelial Dysfunction Markers in Adults with Metabolic Syndrome: A Systematic Review

Artículo de revisión publicado en el Journal of Food and Nutrition Research, 2018, Vol. 6, No. *No. 8, 537-545* disponible online en http://pubs.sciepub.com/jfnr/6/x/x

Disponible online en: http://www.sciepub.com/JFNR/abstract/9541

Indexada en Q3 según SJR y en B según Publindex para el año 2018

DOI:10.12691/jfnr-6-x-x

Journal of Food and Nutrition Research, 2018, Vol. 6, No. 8, 537-545
Available online at http://pubs.sciepub.com/jfnr/6/8/9

DOI:10.12691/jfnr-6-8-9

Effect of Dietary Intervention on Inflammatory and Endothelial Dysfunction Markers in Adults with Metabolic Syndrome: A Systematic Review

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Received July 09, 2018; Revised August 23, 2018; Accepted September 11, 2018

Abstract Chronic low-grade inflammation is associated with metabolic syndrome and obesity and is characterized by high serum concentration of inflammatory and endothelial dysfunction markers. Studies have shown that western diets may increase the risk of diabetes mellitus and cardiovascular disease; however, healthy eating interventions have been also shown to improve the inflammatory state and endothelial function. A relationship between mixed diets and markers of inflammation and endothelial dysfunction has been previously suggested, since some foods have antioxidant and anti-inflammatory activity. Therefore, we conducted a systematic review of randomized clinical trials of parallel-group or crossover design studies published in the English language that evaluated the effects of dietary interventions on inflammatory and endothelial dysfunction markers in adults with metabolic syndrome. The literature search included electronic databases, manual search, and peer-reviewed articles published from 2005 to 2015. Fourteen studies, with a total of 1470 participants, met the inclusion criteria. Dietary interventions ranged from 2 to 52 weeks. Half of the studies reported a positive effect of dietary interventions on inflammatory markers, being C-reactive protein the one most frequently quantified. Compared to control groups, diets rich in polyunsaturated fatty acids reduced serum CRP levels; Mediterranean diets enriched in olive oil and nuts reduced serum IL-6; and a decrease in serum ICAM levels was observed in Mediterranean diet rich in olive oil. Four of the analyzed studies measured serum TNF-alpha levels, which did not exhibit a significant variation among groups.

Keywords: *inflammation, endothelial function, biomarkers, metabolic syndrome, mixed diet ormat, microsoft word template, style, insert, template*

Cite This Article: Elcy Yaned Astudillo-Muñoz, Diana Maria Muñoz-Pérez, and Clara Helena González-Correa1uthor One, "Effect of Dietary Intervention on Inflammatory and Endothelial Dysfunction Markers in Adults with Metabolic Syndrome: A Systematic Review." *Journal of Food and Nutrition Research*, vol. 6, no. 8 (2018): 537-545. doi: 10.12691/jfnr-6-8-9.

1. Introduction

Metabolic syndrome (MetS) is defined as a group of metabolic alterations clinically evidenced by central obesity, reduced serum levels of high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, hypertension, and hyperglycemia [1]. In the majority of cases, MetSis associated with obesity [2] and atherosclerosis [3,4], and is a contributing factor generating non-communicable diseases. Chronic non-communicable diseases (NCD) –such as cardiovascular disease, obesity, and type-2 diabetes mellitus (T2DM)- represent a significant cause of mortality worldwide. Over the past decades, chronic NCD have been associated with chronic low-grade inflammation [4,5,6]. This inflammatory response is mediated by the activation of the transcription factor NF-kB [7], leading to increased expression of proinflammatory and endothelial dysfunction genes; which in turn, increase levels of cytokines derived from adipose tissue and liver [8,9]. As a final result, there is a systemic inflammatory response mediated by C-reactive protein (CRP), inflammatory cytokines (IL-6 andTNF-alpha), vascular cellular adhesion molecules (VCAMs), and intercellular adhesion molecules (ICAM) [10].

C-reactive protein is an acute-phase protein synthesized by hepatocytes stimulated by inflammatory cytokines IL-6 and TNF-alpha [11]. Subtle changes in CRP serum levels are used as a biomarker of subclinical inflammation found in MetS and obesity [12,13,15]. TNF-alpha is associated with insulin resistance [16] by inhibiting translocation of glucose transporters (GLUT-4) to the cellular membrane [17,18]. Adhesion molecules including E-selectin, ICAM-1, and VCAM-1 mediate endothelial cell damage. These molecules are attract macrophages and lymphocytes to the endothelium, produce oxidative stress and increase expression of proinflammatory molecules [19,20]. Inflammatory processes also involve the vascular endothelium [21], which under pathological conditions may lead to atherosclerosis, a critical factor in the development,

progression and clinical manifestation of cardiovascular disease and diabetes [22]. These inflammatory proteins –CRP, IL-6, TNF-alpha, VCAM-1, and ICAM-1- have been previously described as biomarkers to assess the effect of dietary intervention on the inflammatory response and endothelial dysfunction in MetS and obese patients.

Because unbalanced diets may support chronic low-grade inflammation and oxidative stress, previous studies have assessed the effect of diet intervention on these inflammatory markers [23,24]. Decreased levels of these molecules would thus suggest a decrease in chronic NCD risk [25,26,27]. A meta-analysis of 17 clinical studies that included 2300 participants showed that an intervention with Mediterranean diet significantly reduced levels of CRP, IL-6, and ICAM [28].Additional studies suggest that the Mediterranean diet may be effective in reducing the prevalence of MetS and the associated risk of cardiovascular disease [29].

Previous studies have reported an inverse association between fruit and vegetable consumption with serologic levels of inflammatory markers [11]. On one hand, dietary flavonoids, found in fruits and vegetables, have been shown to contribute to the reduction of risk of cardiovascular disease (CVD) [30,31]. Specifically, quercetin –a flavonoid present in fruits and vegetables- has been shown to attenuate TNF-alpha and proinflammatory gene expression, hence reducing the inflammatory response in adipose tissue [32]. Additionally, vegetarian diets have also been found to reduce serum levels of CRP, thus reducing risk of CVD [33]. Interestingly, a study of 3920 participants (≥20 years of age), showed an inverse association of dietary fruit fiber intake with risk of CVD [34].

While several studies focusing on a single type of nutrient or specific diet component [35,36,37], there are few studies that assess the effect of a mixed diet with a variety of component. Therefore, in this review, we analyzed the effect of mixed dietary intervention on inflammatory and endothelial dysfunction makers, as well as its contribution to reducing complications of metabolic syndrome.

2. Materials and Methods

Using the terms "Diet, AND inflammation AND biomarkers", PubMed, Scopus, and Science Direct databases were searched to identify relevant studies published between 2005 and 2015. Additionally, a manual search was performed for those references found in relevant articles. Language was limited to English, as we did not find studies in other languages.

2.1. Inclusion Criteria

Randomized clinical trials of parallel-group or crossover design, which included adults only (≥18 years old), with a body mass index (BMI) ≥25,00 kg/m², and at least one MetS clinical manifestation as defined by the World Health Organization (WHO) [38]. Studies must have had at least two types of dietary interventions that lasted at least two weeks. Our focus was on studies using dietary interventions in which a mixed diet was included, and its effect on inflammatory and endothelial dysfunction markers was addressed.

2.2. Exclusion Criteria

Studies including children, teenagers, pregnant women, participants with rheumatic disease, hypothyroidism, smokers, medicated patients, or patients participating in a physical exercise program were excluded from this analysis.

2.3. Risk of Bias Assessment

The three authors independently assessed risk of bias by using the Cochrane risk of bias tool (Revman 5.3). This tool assesses risk of bias on the following domains: selection bias, performance bias, detection bias, attrition bias. Studies with high risk of attrition bias were not excluded. We judged risk of bias criteria as 'low risk', 'high risk' or 'unclear risk'. Results for assessment of the risk of bias for each domain for each study were compared and disagreements resolved by discussion (Figure 1).

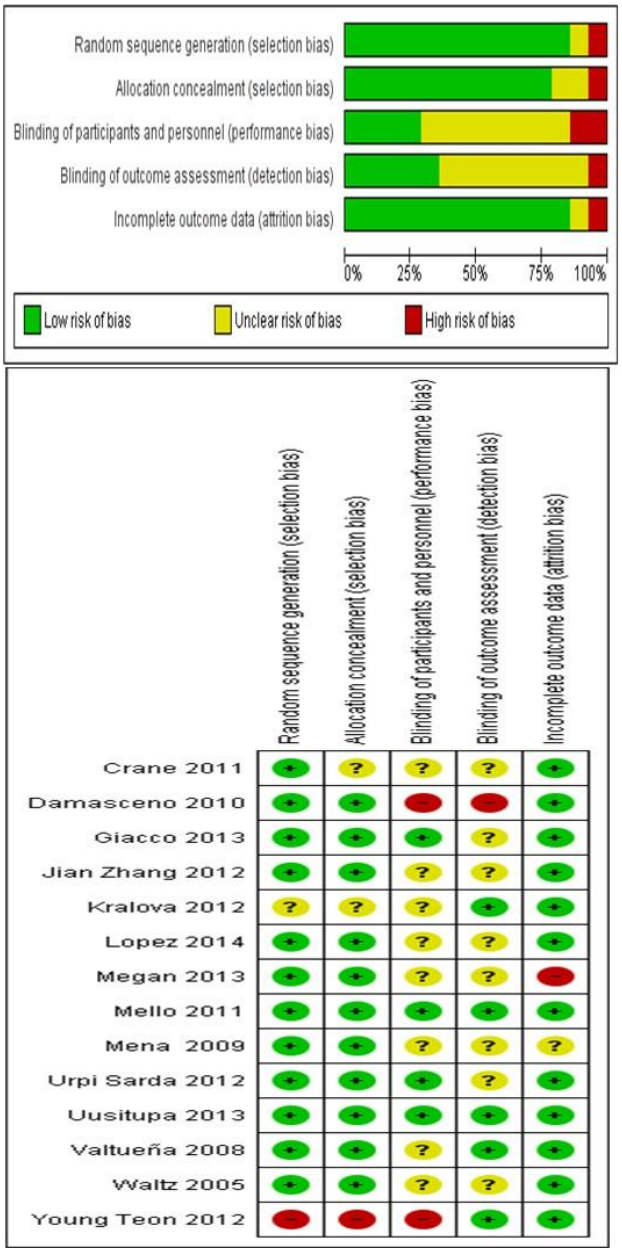

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Revman 5.3

2.4. Data Extraction

Data extraction was performed by two of the researchers of this study, by using a format that included data on study design, participants, type of intervention, comparisons between intervention diets, and outcomes. A third researcher participated if required to resolve differences between the first two researchers.

2.5. Outcomes

Changes in serum CRP levels were designated as primary outcomes of the effect of diet intervention on inflammatory markers. Changes in serum IL-6 and TNF-alpha levels were defined as secondary outcomes. Additionally, changes in serum VCAM and ICAM levels were designated as anoutcome of the effect of diet intervention on endothelial dysfunction.

2.6. Data Analysis

The percent change in serum levels of inflammatory and endothelial dysfunction markers in the intervened and the control groups were calculated and analyzed.

3. Results

3.1. Literature Search and Study

A total of 2052 studies were identified in the searched databases. Of those, 14 studies met the inclusion criteria and accounted for a total of 1470 participants (719 male, 751 female). (Figure 2).

3.2. Characteristics and Selected Studies

As shown in Table 1, 14 studies were included in our analysis. Duration of interventions ranged from 2 to 52 weeks. Sample size varied from 15 and 516 participants, for a total of 1470 (719 male, 751 female). (Table 1)

3.3. Types of Interventions

Of the 14 studies, five compared two interventions to a control group, while the remaining 9 compared one dietary pattern to the control group. Altogether, 33 diets were compared.

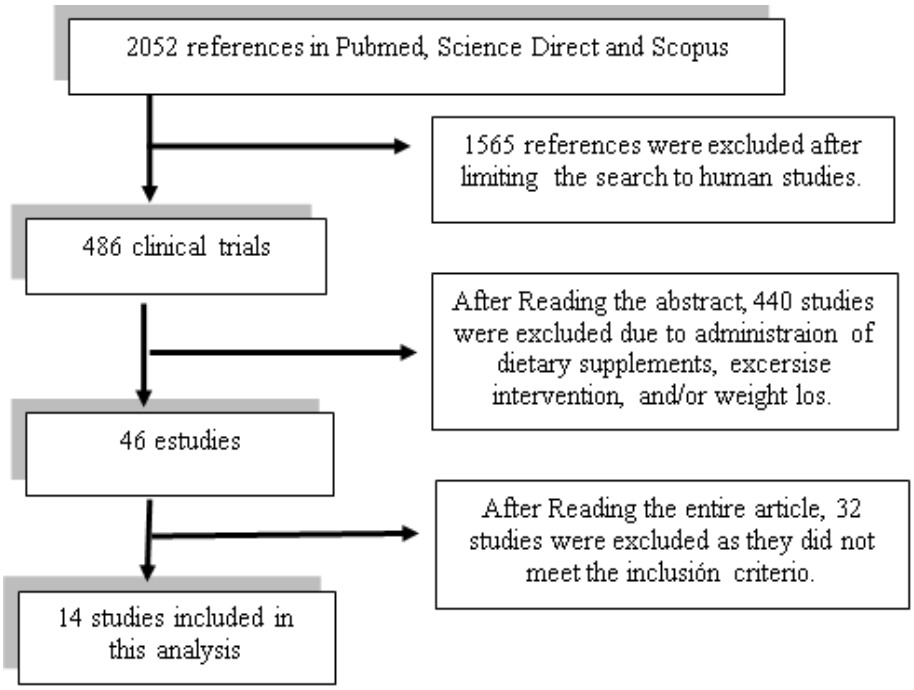

Figure 2. Screening strategy used to identify studies meeting inclusion criteria

Table 1. Summarized effects of diet interventions used in the analyzed studies

Ref	Population	Intervention (s) (n)	Diet	Duration (weeks)	Markers	Baseline	Effect	Conclusion
Mello et al 2011	104 participants Age: 40 - 70 years MetS	HD (36), WGED (34) vs CD (34)	HD: CHO 48.2% protein 21.6%, fat 30.2%, fiber 36.5g WGED: CHO 47.2% protein 21.7% fat 31.1%, fiber 26.6g CD: CHO 47.2%, fat 31.9%, protein 29.2%, fiber 17.6g	12	CRP mg/L	1.4 vs. 1,5 vs. 1,4	-0,14 vs -0,3 vs -0,11 (p=0,04)	WGED led to significant reduction
					TNFa pg/ml	0.6 vs. 0,7 vs. 0,6	0,03 vs 0,063 vs. 0,018 (p=0,35)	No significant difference
					ICAM ng/ml	601 vs. 602 vs. 596	607 vs 595,9 vs 603,8 p= (0,89)	No significant difference
					IL-6 pg/ml	1.6 vs. 1,4 vs. 1,3	-0,11 vs 0,04 vs 0,039 (p=0,66)	No significant difference

Ref	Population	Intervention (s) (n)	Diet	Duration (weeks)	Markers	Baseline	Effect	Conclusion
Giaco et al. 2013	24 participants. Ages: 40-65 years. MetS	WG (62) vs CD (62)	WG: CHO 48%, protein 18.7%, Fat 31%, fiber 32.6g CD: CHO 49%, protein 17.8%, fat 30.8%, fiber 19.8g	12	CRP hs mg/L	1.95	-0,59 vs 0,21 (p=0,16)	No significant difference
					TNFa pg/ml	0.73 vs. 0,62	.-0,05 vs 0,1 (p=0,84)	
					IL-6 pg/ml	1.42 vs. 1,41	0,12 vs 0,02 (p=0,52)	
Jian Zhang et al 2012	126 participants. Ages: 35- 70 years. MetS	Sa (32) vs He (29) vs Po (33) vs CD (32)	52.1% protein 15% fat 32.5% Salmon CHO Herring: CHO 52.1% protein 15.5% fat 32.4% Pompano: CHO 54.2 protein 14.1% fat 31.7% CD: CHO 54.6% protein 54.2% fat 31.1%	8	IL-6 pg/ml	268.1	-23,1 vs -17,3 vs -17,8 vs -3,5 (p=0,5)	Intake of salmon decreased TNFa and IL-6 levels; intake of herring decreased TNFa and increased adiponectin; and intake of pompano did not. (Highest EPA and DHA content). However, there was no significant statistical difference between groups.
					TNFa pg/ml	13.3	-1,5 vs -1,1 vs 1,0 vs 0,2 (p=0,36)	
					ICAM ng/ml	271	-10,3 vs -18 vs -1,7 vs -11,5 Not reported	
					VCAM ng/ml	319.2	38,6 vs. -32,5 vs 18,6 vs 63,9 Not reported	
					CRP mg/L	2	-0,02 vs -0,13 vs -0,13 vs 0,08 Not reported	
					Adiponectin ug/ml	6.7	0,7 vs 0,9v. 0,6 vs 0,4 (p=0,8)	
Mena et al 2009.	106 participants. Ages: 55 - 80 years. MetS	MD+VO (35) vs MD+N (35) vs LFD (36)	MD+VO: protein 17.8%, CHO 49.9%, fat 35.6%. MD+N: protein 16.3%, CHO: 41.6% fat 37.7%. LFD: protein 19.3%. CHO 42.4%, fat 34.2%	12	PCR mg/L	4,0 vs 2,2 vs 2,8	-1,6 vs 0,35 vs 1,1 (p=0,02)	Both MD showed significant effect
					IL-6 pg/ml	6,8 vs 6,8 v 5,9	-1,09 vs -0,82 vs 1,41 (p=0,001)	Both MD showed significant effect
					ICAM ng/ml	290 vs. 270 vs 239	-58 vs -32,4 vs 76,5 (p=0,003)	Both MD showed significant effect
					VCAM ng/ml	1033 vs 962 vs 1023	-124 vs -20 vs 204,6 (p=0,001)	MD+VO showed significant effect
Valtueña et al 2008	34 participants. Average age: 61 years. Healthy subjects	HT (33) vs LT (33)	HT: protein 14.4%, fat 31.7%, CHO 50.5% vitC 423 mg/day) 2 grp LT: 13.8%protein, fat 33%. CHO 47.5%. vit c 91.7 mg/day)	2 weeks each diet. Cleanse halfway through the study	High sensitivity PCR	3mg/l	-0,72 vs 1,5 (p=0,007)	HT diet showed significant effect
Lopez et al 2014.	96 participants. Average age: 50 years. MetS	RD (48) vs CD (48)	RD: 30% de protein CHO 40%. fat 30% CD: 55%CHO. 30% fat 15% protein	8	IL-6 pg/ml	2.71 vs. 2,61	0,08 vs -0,05 (p=0,71)	No significant changes in inflammatory markers, but LDL cholesterol was significantly reduced. All three diets promoted vegetable intake, and restricted intake of dairy, red meats, and eggs
					TNFa pg/ml	0.76 vs. 0,66	0,02 vs -0,08 (p=0,11)	
					CRP mg/L	3.2 vs. 3,19	0,19 vs -0,84 (p=0,27)	
Megan et al 2013.	33 participants. Ages 21- 62 years. MetS	HFLCD (18) vs LFHCD (15)	**HFLCD:** CHO 10.4% fat 56% Protein 33.5% **LFHCD:** CHO 60%. fat 25%. protein 15%	12	Adiponectin ug/ml	4.01 vs. 4,59	0,4 vs -0,18 (p=0,045)	HFLCD diet decreased CRP and increased adiponectin
					CRP hs mg/L	5.62 vs. 6,94	-1,68 vs -0,19 (p=0,03)	

Ref	Population	Intervention (s) (n)	Diet	Duration (weeks)	Markers	Baseline	Effect	Conclusion
Crane et al 2011.	49 participants Ages: 52-65 years, Obese	10 VP (49) vs 5VP (49) vs (49)	**2VP:** 130g **5VP**: 287g **10VP:** 614 g	Each intervention: 3 weeks. 4 weeks cleanse in between treatments.	CRPhs mg/L	2.5	-0,17 vs -0,08 (p=0,78)	No significant difference between 5 or 10 vegetable servings compared with 2 servings.
Waltz et al 2005	63 participants. Average age: 32 years. Healthy subjects	2FV (21) vs 5FV (21) vs 8FV (21)	**2FV:** CHO 49.8% protein 14.9% fat 35.3% **5FV:** CHO 45.4% protein 15.3% fat 35.3% **8FV:** CHO 47.7% fat 35.3% protein 15%	4	PCR hs mg/L	1.51	1,69 vs 0,84 vs -0,46 (p=0,05)	significant decrease in CRP levels with 8 fruit/vegetable servings per day
Urpisarda et al 2012.	516 participants. Ages 54 -79 years. MetS	MD+VO (178) vsMD+N (175) vs LFD (163)	**MD+VO:** protin 17.8% CHO 49.9% grasa 35.6%. **DM+N:** protein 16.3% CHO: 41.6 fat 37.7% **LFD:** protein 19.3%. CHO 42.4% fat 34.2%	24	IL-6 ng/L	0.9 pg/ml	-0,23 vs -0,33 vs 0,13 (p=<0,001)	Both MD significantly decreased inflammatory markers compared with low fat diet.
					ICAM ng/ml	258	-10 vs -2,0 vs 24 (p=0,001)	
Damascene o et al 2011.	26 participants. Age: 25 - 75 years. Hypercholesterolemia	VOOD (26) vs ND (26) vs AD (269)	**VOOD:** CHO 49% prot 16% fat 32.5% fiber 25g **ND:** CHO 49% protein 16% fat 32.5%. fiber 25g **AD:** CHO 48.5% protein 17% fat 33% fiber 29g	4	ICAM ng/ml	291	-19 vs -53 vs -31 (p=0,182)	No significant changes in inflammatory markers, but LDL was significantly reduced. All three diets promoted vegetable intake, and restricted intake of dairy, red meats, and eggs.
					VCAM ng/ml	670	60 vs 154 vs 90 (p=0,18)	
					PCR hs	2.1	-0,4 vs -0,2 vs -0,4 (p=0,241)	
Uusitupa et al 2013.	166 participants Average age: 55 years.	ND (96) vs HND (70)	**ND:** CHO 46.8% prot 175% fat 31.7% **CD:** CHO 44.6% prot 16.2% fat 35.2%	6 months	PCR mg/L	2,6 vs. 2,4	0,1 vs -0,1 (p=0,18)	Significant changes in other markers including IL-1Ra and non-HDL
					IL-6 ng/L	1,53 vs. 1,51	0,16 vs 0,08 (p=0,44)	
					adiponectin HMW mg/l	5.43 vs. 4,72	0,2 vs -0,04 (p=0,81)	
Kralova et al 2013.	15 participants Age: 45 years and older. Dyslipidemia	PUFA (15) vs SAFA (15)	**PUFA:** CHO 47% fat 40% **SFA:** CHO 46% fat 42%	3	CRP mg/L	6.61 vs. 2,95	-4,05 vs 0,35 (p=<0,01)	PUFA diet significantly reduces CRP levels

Ref	Population	Intervention (s) (n)	Diet	Duration (weeks)	Markers	Baseline	Effect	Conclusion
Jee Young Yeon et al 2012	22 participants, Age: 19-29 years. Overweight	HVFD (26) vs LVFD (26)	**LVF:** CHO 55% fat 25% protein 18% **HVF:** CHO: 61.3%. fat 22.5%. protein 17.2%	26 weeks. 2 weeks each diet. 2 weeks cleanse	CRP mg/L	0.56 vs. 0,54	0,16 vs 0,21 (p=0,064)	No significant changes. However, culture of PBMCs stimulated with LPS showed decreased cytokine (IL-1, IL-6) production in participants in the HVF diet
					IL-6 pg/ml	3.53 vs. 3,65	-0,08 vs - 0,57 (p=0,14)	
					Adiponectin ug/ml	8.56 vs. 8,23	0,66 vs -0,14 (p=0,36)	

HD, healthy diet; CHO, carbohydrates; WGED, whole grain diet; CD, control diet; CRP, C-reactive protein; TNFa, tumor necrosis factor alpha; IL-6, interleukin 6; ICAM, intercellular adhesion molecule; WG, whole grain; VCAM, vascular cell adhesion molecule; Sa, salmon; He, herring; Po, pompano; MD, Mediterranean diet; VO, virgin olive oil; N, nuts; LFD, low-fat diet; HT, high-TAC (Total antioxidant capacity); LT, low-TAC (Total antioxidant capacity); RD, RESMENA diet; ND, Nordic diet; AD; HND; HFLCD, high-fat low-carb diet; LFHCD, low-fat high-carb diet; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; 2VP, 2 vegetable portions; 5VP, 5 vegetable portions; 10VP, 10 vegetable portions; HVFD, high vegetable fruit diet; LVFD, low vegetable fruit diet. HMW alto peso molecular.

The dietary interventions included a wide range of mixed diets: Mediterranean diet supplemented with mixed nuts or virgin olive oil; high-fat low-carb diet; low-fat high-carb diet, with whole or refined grains with different types of proteins; different amounts of fruits and vegetables; with different fatty acids; with high and low glycemic index, and with high and low antioxidant power.

3.4. Significant Differences between Dietary Intervention and Control Groups

3.4.1. Primary Outcomes: Variation in Serum CRP Levels

Of the analyzed studies, 13 of 14 measured serum CRP levels. Six studies showed a significant difference between dietary intervention and control groups, being greater in the control group. Particularly, the study by Kralova et al. (2013), detected the greatest changes. Two diets were compared in the intervention group: one diet was rich in polyunsaturated fatty acids, and the second one was rich in saturated fatty acids. The authors reported that the diet rich in polyunsaturated fatty acids reduced serum CRP levels in 4,05 mg/l (6,6 to 2,56mg/l), while the control diet had the opposite effect and instead increased serum CRP levels by 0,35 mg/l (2,95 to 3,3 mg/l).

3.4.2. Secondary Outcomes: Variations in TNF-alpha Serum Levels

Of the analyzed studies, 4 of 14 measured serum TNF-alpha levels. In these four studies, levels of TNF-alpha did not exhibit a significant difference among groups.

3.4.3. Secondary Outcomes: Variations in IL-6 Serum Levels

Of the analyzed studies, 6 of 14 measured serum IL-6 levels. Three studies showed a significant difference between dietary intervention and control groups. Specifically, in the study by Urpisarada et al. (2012), two types of Mediterranean diets were compared: one rich in olive oil and the other one enriched with nuts, which were compared with a low-fat diet. Mediterranean diets enriched in olive oil, and nuts achieved a reduction in serum IL-6 levels of 1,09pg/ml and 0,82 pg/ml respectively compared to the control group, which increased 1,41pg/ml.

3.4.4. Secondary Outcomes: Variations of Serum Levels of the Endothelial Dysfunction Markers VCAM and ICAM

Of the analyzed studies, 4 of 14 assessed markers of endothelial dysfunction. Two of those studies showed a significant difference between dietary intervention and control groups. Specifically, in the study by Urpisarda et al. (2012) two types of Mediterranean diets were compared: one rich in olive oil and the other one enriched with nuts, which were compared with a low-fat diet. A decrease in serum ICAM levels (10ug/l) was observedin the Mediterranean diet rich in olive oil compared with the low-fat diet, which exhibited an increase in ICAM levels of up to 24ug/l. An additional study by Mena et al. (2009) showed that while the control group exhibited increase in serum ICAM (76,5ug/l) and VCAM (204,4ng/l) levels, a Mediterranean diet rich in olive oil led to a decrease in both serum ICAM (58 ug/l) and VCAM (124 ng/l) levels.

3.5. Study Limitations

One limitations of our study is the heterogeneity among the analyzed studies. There was diversity among the analyzed inflammatory and endothelial dysfunction markers, as well as types of diets, duration of intervention, and age of participants. Due to this heterogeneity, we were not able to perform a meta-analysis of the data provided by these studies.

4. Discussion

In this review, we aimed to analyze the effect of mixed dietary intervention on inflammatory and endothelial

dysfunction makers, as well as its contribution to reducing complications of metabolic syndrome. We found that 50% of the studies showed positive results of dietary intervention on reducing inflammatory makers, being CRP the one most commonly quantified. The changes in dietary patterns can be grouped into three categories:
1) replacement of refined grains by whole grains,
2) reduction of saturated fatty acids (SFA) and increase of polyunsaturated fatty acids (PUFA), and 3) increase in fruit and vegetable intake.

Regarding the replacement of refined grains by whole grains, an intake of 113 g/d of whole grains and 29g/d of fiber significantly reduced serum CRP [42] levels. This dietary intervention also included berries, vegetables, and fish. Furthermore, the study by Vitaglione et al. 2005 found a decrease in serum TNF-alpha levels with an even lower amount of whole grains (70 g/d). However, a similar study containing comparable intake of whole grain and fiber, 112g/d and 30 g/d respectively, did not show a decrease in either CRP nor IL-6 [44]. In agreement with that study, Giaco et al. (2013) did not observe significant changes in serum CRP, TNF-alpha, or IL-6 levels. Similarly, an additional study comparing an intake of 60 or 120 g/d of whole grains did not report any changes in serum CRP, IL-6, ICAM or VCAM levels.

These discrepancies may be explained, on one hand, by the diversity of grains (oats, rye, or wheat bran), as they contain different amounts of ferulic acid, the phenolic component of whole grains [43,46]. On another hand, the amount and quality of fiber also vary among these grains. Additionally, the duration of the interventions was of different lengths, which may ultimately have an effect on the outcome.

Phenolic components provide anti-inflammatory and antioxidant properties by scavenging free radicals and activating redox enzymes in cells and tissues [47]. However, there are contradictory results regarding the role of whole grains in inflammation. It is possible that in addition to the content of phenolic compounds, the amount of fiber also contributes to the anti-inflammatory effect of whole grains [47]. Fiber may contribute to the changes observed in the inflammatory markers analyzed in studies in which there was an increased intake of whole grains, fruits, and vegetables. The effect may be mediated by the fermentation process in the intestinal microbiota, producing short chain fatty acids, which have anti-inflammatory properties [48].

Regarding changes in dietary patterns in which intake of SFA is reduced and replaced by PUFA, the study by Kralova et al. (2013) reported that a diet rich in PUFA led to a significant decrease in serum CRP (61.3%) levels. In that study, while fat represented 40% to 42% of the total energy, the percentage of SFA and PUFA were significantly different between dietary interventions, being one composed by 29% SFA and 8% PUFA, and the other 6% SFA and 25% PUFA. An additional study by Tee Voon et al. (2011) compared a dietary intervention with a lower amount of total fat (30%) of the total energy (20%) as saturated fats (palmitic, lauric, and myristic acids) to one with 20% PUFA (olive oil) and found no significant differences in serum CRP, IL-6, or TNF-alpha levels.

The study by Ruth et al (2013) showed that, compared to a low-fat high carb-diet (LFHC), a high-fat low-carb diet (HFLC) may be more efficient in reducing serum CRP levels and increasing adiponectin levels. However, that study has significant limitations due to the high desertion rate (48,5%). The Multi-Ethnic Study of Atherosclerosis [51] reported an inverse association between PUFA and serum CRP and IL-6 levels in obese participants compared to normal weight participants. This observation may be partly due to variations in diet and absorption processes. Additional studies in which 5% of the SFA energy was replaced by PUFA showed a risk of coronary heart disease lower than 13% [52,53,54].

Fatty acids saturated may act as Toll-like receptor (TLR) 2 and TLR4 ligands, activating inflammatory processes via activation of NF-kB transcription factor, which leads to synthesis of adhesion molecules [54]. In contrast, PUFA, especially omega-3 and omega-9, may inhibit such process by acting as PPAR-gamma ligands [55]. These acids decrease adhesion molecule synthesis, which may diminish migration of leukocytes and smooth muscle cells towards the endothelium, delaying the atherosclerotic process [39,56,57] and thus improving endothelial function [58]. Therefore, increased PUFA (omega-3) intake and decreased SFA intake may play a significant role in the reduction of serum inflammatory markers [40,41]. In agreement with these results, the study by Esposito et al, 2004 showed that increased PUFA intake – as eicosapentaenoic acid (EPA) and docosahexoenoic acid (DHA)- was associated to a reduction in arachidonic acid, a precursor of proinflammatory molecules such as prostaglandins, leukotrienes and thromboxanes [59,60].

Finally, regardingchanges in dietary patterns in which fruit and vegetable intake was increased, a study comparing an intake 800 g (8 portions) with 200 g (2 portions) observed a decrease of 32% in serum CRP levels in the higher fruit and vegetable intake diet [61]. In contrast, a dietary intervention containing 614 g of vegetables did not show an effect on serum inflammatory markers [62].

In the study by Valtueña et al. (2008), including a greater variety of fruits and vegetables (550 g), 200 ml of fruit juice, and additional antioxidant foods in the dietary intervention led to a reduction of 24% in serum CRP levels. In contrast, a dietary intervention with the same total amount of fruit and vegetables but with limited variety, and with less powerful antioxidant foods showed an increase of 62,5% in serum CRP levels.

In this review, we have analyzed the effects of different dietary interventions on the most frequently reported inflammatory (CRP, IL-6, TNF-alpha) and endothelial dysfunction (ICAM and VCAM) markers. The latter were quantified in 4of the 14 identified studies, being reduced by dietary intervention in 2 of the studies [40,41]. However, additional markers not included in this review were also quantified in the analyzed studies. Giacco et al. 2014 used a dietary intervention rich in whole grains and found a decrease in postprandial insulin and triglycerides. Likewise, Damasceno et al. (2011) showed a decrease in low-density lipoprotein (LDL) cholesterol by providing a Mediterranean diet rich in olive oil, almonds or nuts; Urpisarda et al. (2012) observed changes in IL-1 receptor and non-HDL cholesterol. Furthermore, Yeon et al (2012), analyzed the effects of high and low vegetable-fruit (VF) diets in overweight women by isolating and culturing peripheral blood mononuclear cells (PBMCs),

and subsequently activating them with lipopolysaccharide (LPS) and quantifying pro-inflammatory molecules. In that study, PBMCs of participants in the high-VF diet produced lower amounts of proinflammatory molecules IL-6 and IL-1 beta. An additional study compared the effect of different kinds of fish intake with chicken and pork intake, and found that 80 gr of salmon reduced to a greater extent serum TNF-alpha, and increased adiponectin levels [67].

Altogether, these studies suggest that a single marker may not be enough to determine the effect of a given dietary intervention on inflammatory and endothelial dysfunction markers. Moreover, it is likely that one or several diet nutrients may selectively improve one, or several, of these markers. Plausibly, the synergistic effect of nutrients and diets in which different food replacements (mixed diets) are simultaneously substituted(refined grains with whole grains, food with greater PUFA than SFA, increased fruit and vegetable intake, greater fish than meat intake) (66), such as the Mediterranean diet, lead to significant decrease on serum levels of CRP (40%), IL-6 (15%), and endothelial dysfunction markers ICAM (20%) and VCAM (25%) [40,41]. Additionally, mixed diets consisting of fruits, vegetables, and whole grains increase polyphenol intake, which contribute to reduce oxidative stress in tissues, thus providing a protective effect on patients with risk of CVD [24,68,69]. Furthermore, Lee et al. 2014 studied the effect of different dietary patterns in a Korean population of 7574 participants and found an inverse relationship between raw vegetable intake (96,3 g/d) and serum CRP levels. This effect was attributed to the association of vitamins, fiber, antioxidants, and polyphenols present in these foods.

In this review we were unable to determine whether one dietary pattern has more beneficial effects on inflammatory and endothelial dysfunction markers than another. This is likely due to the heterogeneity of quantified markers, types and duration of interventions, as well as age of participants. The most striking common feature was that interventions including mixed diets may be the most promising approach to reduce inflammatory and endothelial dysfunction markers. To this end, in order to increase adherence to healthy dietary patterns, it is important to provide a varied diet that is suited to foods available to each region. To this end, in order to increase adherence to healthy dietary patterns, it is important to provide a varied diet that is suited to foods available to each region.

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CAPITULO II: Postprandial lipid profile in young Colombian people. A comparison of two breakfasts

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Artículo de investigación publicado en el Journal Nutrición Clínica y Dietética Hospitalaria. Nutr. clín. diet. hosp. 2019; 39(2):97-103 DOI: 10.12873/392muñoz .

Disponible online en: https://www.revistanutricion.org/articles/postprandial-lipid-profile-in-young-colombian-people-a-comparison-of-two-breakfasts.pdf

Indexada en Q4 según SJR y en C según Publindex para el año 2018.

Recibido: 6/marzo/2019. Aceptado: 30/junio/2019.

nutrición clínica y Dietética Hospitalaria

Artículo Original

Nutr. clín. diet. hosp. 2019;39(2):97-103
DOI: 10.12873/392muñoz

Postprandial lipid profile in young colombian people. A comparison of two breakfasts

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Recibido: 6/marzo/2019. Aceptado: 30/junio/2019.

ABSTRACT

The aim was to compare the postprandial lipid profile of university students who ate a regular breakfast of the Colombian Andean region, high in saturated fats and low in complex carbohydrates, compared with an experimental breakfast with low fat content and high in complex carbohydrates and its relation with anthropometric measurements. 75 university students consumed one of the two breakfasts after a 12-hour fast. A complete lipid profile was performed in a fasted state, three and six hours after breakfast ingestion. Of the 75 patients, 11 were withdrawn, 28 people consumed the experimental breakfast and 36 the usual one. There was no significant difference between the two groups; however, there was a tendency to decrease the levels of all the components of the lipid profile in the experimental breakfast, except for High density lipoprotein (HDL). The Area under the Curve (AUC) did not show differences between breakfasts. The body mass index (BMI) and the waist / hip ratio (WHR) showed an inverse relationship with HDL and a direct relationship with Low density lipoproteins (LDL). In conclusion, there were not differences in the acute effect of both breakfasts, possibly due to factors such as smoking, exercise, sedentary lifestyle, type of food used in the diet, variables that were not discriminated in this study. The main contribution of this study is the description of the behavior over time of the lipid profile variables and their relationship with the anthropometric variables. It is possible that the effect of these diets is likely to be significant in the long term.

KEYWORDS

Lipids, blood, postprandial, profile, healthy people.

LIST OF ABBREVIATIONS

BMI: Body mass index.

AUC: Area under the Curve.

WHR: Waist / hip ratio.

LDL: Low density lipoproteins.

Non-HDL: Non-high density lipoproteins.

HDL: High density lipoprotein.

TG: Triglyceride.

VLDL: Very low density lipoprotein.

apoA, apoB: Apoproteins A, B.

TC: Total Cholesterol.

INTRODUCTION

In recent decades the term postprandial lipemia has been used to represent the variation of triglycerides after the absorption of a high-fat meal[1]. In addition, the postprandial lipid profile allows to measure the different lipoprotein frac- tions after ingestion and absorption of food[2]. Studies show that a postprandial lipid profile provides more significant information compared with a fasting lipid profile, since in the postprandial state both hepatic and intestinal lipoproteins are found[2]. It has been shown that a fat-rich meal consumes 30 to 60 grams of lipids, after which the triglycerides in a healthy person show an elevation in the first 1-2 hours. Subsequently, a maximum peak between the 3rd and 4th hour is obtained with a return to the basal state between

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the 6th and the 8th hour[3,4]. Very low density lipoproteins, or VLDL, increase after ingestion and remain elevated in blood around 3.6 hour[5]. In contrast, there may be a slight de- crease in the low density lipoprotein (LDL), non-high density lipoprotein (NonHDL) and total cholesterol, especially in the first 4 hours after consuming the food but this has been associated with the intake of water that dilutes the blood components[6]. Postprandial lipemia is determined by the levels of preprandial triglycerides and also by the quality and quan- tity of lipids ingested[7,8]. A meal high in polyunsaturated fatty acids, generates a lower lipemia compared to an intake of saturated and monounsaturated fatty acids[8]. It is therefore the elevation of triglycerides and their respective transport lipoproteins (chylomicrons and VLDL), independent of other lipids, which determine postprandial lipemia as a risk factor for the generation of atherosclerosis, and the prediction of acute myocardial infarction[9,10].

The average person spends around 16 hours in the postprandial state and a high lipemia in this period can generate a decrease in high density lipoprotein (HDL) cholesterol, promote the accumulation of LDL, and generate pro-inflammatory and prothrombotic states[11]. People with metabolic syndrome have clearance of lipoproteins is diminished, In this situation, the probability that these begin to generate atherosclerotic processes, is greater because triglycerides begin to replace LDL in this physiopathological process[9]. In contrast, if we could develop better diets, implement them in healthy subjects, we could decrease not only the maximum peaks of lipemia, but the acceleration of the atherosclerotic disease. In this way you could have a valuable tool for the prevention of cardiovascular disease.

That is why the objective of this study was to compare the postprandial lipid profile of university students who ate a regular breakfast from the Andean region of Colombia, rich in saturated fats and low in complex carbohydrates, with the postprandial profile of young people who ate a breakfast with low fat content and rich in complex carbohydrates, in order to analyze the behavior of the different components of the lipid profile.

MATERIALS AND METHODS

Ethical Declarations

The experimental protocol was approved by the ethics committee of the Universidad de Caldas and was developed in accordance with the declaration of Helsinki (1964), revised in Tokyo (1975), Venice (1983) and Hong Kong (1989). In addition, Colombian resolution No. 008430 of October 4, 1993, which establishes the norms for health research, was taken into account. The proposal was classified in the research category with minimal risk. Before initiating the study, each participant signed an informed consent.

Subjects

The participants were volunteers, from the Universidad de Caldas and the Universidad Libre of Pereira, Colombia between the months of July to December 2016. They included university students between 18 and 35 years who were not consuming lipid-lowering drugs or had diagnoses of dyslipidemia, hyper or hypothyroidism, obesity or other chronic diseases. We also excluded people who in fasting had a triglyceride level greater than 150 mg / dl, or were women in pregnancy or lactation.

Study design

This is an experimental, parallel, randomized, controlled, single-blind study with convenience sampling. The participants went to the respective universities, after a 12-hour fast and were randomly assigned to consume one of two types of isocaloric breakfast (579.5 Kc). The experimental breakfast included foods with a high content of complex carbohydrates and low saturated fats. The usual breakfast was high in saturated fat and low in complex carbohydrates. The foods for each breakfast are listed below.

Experimental Breakfast: 100 g bananas, low fat milk (1%) 200 ml, fresh cheese 30 g, corn arepa 30 g, oat flakes 40 g, walnuts 10 g, peanut 10 g, panela 5 g, olive oil 3 ml.

Usual Breakfast: white sugar 10 g, whole milk (3.3%) 120 ml, scrambled egg 100 g, salt 1 g, butter 10 g, coffee 3 g, white bread 56 g, sausage 30 g. (Table 1) describes the percentage of adequacy of the macronutrients and the grams of the different types of lipids obtained through the software Nutritionist Pro®, licensed to the Universidad de Caldas.

Through interrogation, it was found that each student had complied with a 12-hour fast after which a first blood sample was collected. A second and third samples were obtained at 3 and 6 postprandial hours. In all three samples the lipid pro-

Table 1. Percentage adequacy of the macronutrients and type of lipids used in the diets.

Experimental Breakfast		Usual Breakfast	
Carbohydrates	56,1%	Carbohydrates	31,5%
Proteins	14,5%	Proteins	17,7%
Fat	29,4%	Fat	50.8%
MUFA	6,4 g	MUFA	11,4 g
PUFA	7.1 g	PUFA	3,8 g
SAFA	3.5 g	SAFA	13,9 g

MUFA - Monounsaturated fatty acids; PUFA - Polyunsaturated Fatty Acids; SAFA - Saturated Fatty Acids.

file was measured (LDL, HDL, total cholesterol, TG, VLDL and NonHDL).

Anthropometric measurements

Weight, height, abdominal and hip perimeters, and subcutaneous fat folds were measured according to the protocol established with Lohman *et al* 1988. With these variables were calculated the BMI, the waist / hip index and the percentage of fat bodily.

Lipid profile and laboratory tests

The samples were collected in vacuum tubes. The serum, separated from the erythrocytes by centrifugation (3500 RPM x 15 minutes at 4 ^{0}C) was stored at -80 ^{0}C for further analysis of the lipid profile. Total cholesterol, TG, LDL and HDL were analyzed in a COBAS 6000 from Roche. Non HDL cho- lesterol was obtained by subtracting HDL from Total choles- terol and VLDL was calculated with the TG / 5 ratio.

Statistic analysis

The analysis of the data was made with the statistical software SPSS® version 24.0, licensed to the Universidad de Caldas. The sample size calculation was obtained taking into account an alpha error of 5% and a beta error of 20%. The result indicated that a minimum of 10 individuals per group was required to obtain a power greater than 90%. All the descriptive statistics presented were expressed as mean +/- standard deviation (Table 2).

The normality or not of the anthropometric data was determined by means of the Shapiro-Wilk test. Subsequently, the Student's T test or the Mann-Whitney U test were ap- plied for parametric or nonparametric data, respectively, in order to determine the differences between the two groups. In addition, a matrix of bivariate correlations was developed to investigate the relationship of these variables with labo- ratory tests.

Likewise, the normality of all the laboratory variables was verified: lipid profile (total cholesterol, LDL, Non HDL, HDL, triglycerides and VLDL) with the Shapiro-Wilk test. To verify that both groups entered the same conditions, the Student t test was applied to the fasting samples (Hour 0) of each variable. After each variable was applied an Analysis of variance for repeated measures (ANOVA), in order to establish the change in time (Hours 3 and 6) of each of the breakfast groups in the postprandial period.

In addition to the postprandial lipids that were measured at each point of time (0, 3 and 6 hours) the area under the

Table 2. Initial conditions of both groups according to breakfast.

	Units	Experimental Breakfast				Usual Breakfast				
		Mean +/- SD	Minimum	Maximum	CI 95%	Mean +/- SD	Minimum	Maximum	CI 95%	p value
n		28				36				
Age	Years	21,8 +/- 3	19	29	20,62 : 23,02	20,7 +/- 2,87	18	32	19,7 : 21,6	0,06
Weight	kg	62,5 +/- 8,3	45,6	77,2	59,2 : 65,7	61,1 +/- 11,6	41,4	83,9	57,1 : 65,06	0,59
Size	m	1,67 +/- 0,09	1,47	1,84	1,63 : 1,71	1,65 +/- 0,9	1,48	1,85	1,62 : 1,68	0,39
BMI	kg/m^2	22,33 +/- 2,6	16,6	28,2	21,3 : 23,3	22,3 +/- 3,37	16,04	29,6	21,1: 23,4	0,96
Fat	%	23,74 +/- 7,3	11,3	36,9	20,9 : 26,5	25,9 +/- 6,3	10,8	38,03	23,7 : 28,09	0,205
WHR		1,01 +/- 0,37	0,51	1,96	0,87 : 1,16	0,85 +/- 0,30	0,55	1,75	0,75 : 0,96	0,05
cTotal	mg/dl	164,2 +/- 23,5	119	217	155,07:173,3	172,5 +/- 17,5	144	205	166,5:178,4	0,11
cHDL	mg/dl	49,4 +/- 10,9	32,8	76	45,2 : 53,7	49,9 +/- 10,6	28,1	74,6	46,2 : 53,5	0,88
cLDL	mg/dl	99,7 +/- 24,9	51,1	144	90,06 : 109,4	109,8 +/- 22,6	67,4	155,5	102,2: 117,5	0,09
cVLDL	mg/dl	15,9 +/- 5,3	7,6	25,4	13,9 : 18,03	16,05 +/- 4,1	7,6	26,6	14,6 : 17,4	0,94
cNoHDL	mg/dl	112,07 +/-22,6	64,8	156,5	103,2 : 120,8	112,7+/- 22,1	81	165,3	115,2:130,2	0,06
Tg	mg/dl	79,9 +/- 26,5	38	127	69,6 : 90,1	80,2 +/- 20,9	38	133	73,2 : 87,3	0,94

SD - standard deviation; BMI - body mass index; WHR - Waist / hip Ratio; CI – confidence interva.

curve (AUC) was measured through the trapezoidal method. The effect of the breakfasts on the AUC was compared with the Student t test for independent samples. A statistically significant p value of less than 0.05 was considered for all tests ($p < 0.05$).

RESULTS

Of the 75 initial participants, 3 withdrew during the course of the study and 8 because they had fasting triglycerides greater than 150 mg / dl. With the 64 resulting participants two groups were created, group 1 that received the experimental breakfast (Breakfast 1) and was composed of 28 people (14 men and 14 women), and group 2 that received the usual breakfast of the Andean region (Breakfast 2), had 36 people (13 men and 23 women). The variables size, weight, BMI and percentage % of fat presented a normal distribution, and no statistically significant difference was found between the two groups. The variables age and waist hip index were not normally distributed. There was no difference by age between both groups. The waist-hip index showed a marginal difference ($p = 0.050$) between the two groups (Table 3).

The laboratory tests taken on fasting showed a normal distribution and no significant differences were found in any of the lipid profile variables between the two groups at the beginning of the study (Table 2). In the ANOVA, there was a tendency to decrease total cholesterol, LDL, Non HDL, TG and VLDL in the group with the experimental breakfast of the Andean region compared with the usual breakfast of the Andean region, although it was not statistically significant. This trend was not observed for HDL.

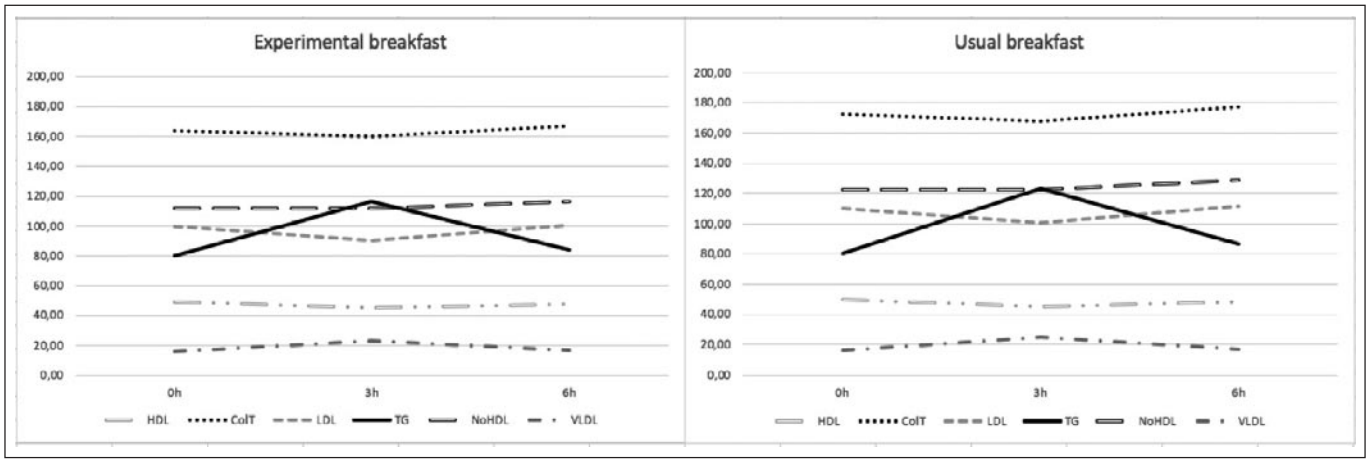
Figure 1 (A and B): shows the behavior over time of the levels of the laboratory variables of both breakfasts. There is a marked increase in TG and VLDL at 3 hours, with a decrease in baseline at 6 hours. With a difference in the average between breakfast (usual breakfast - experimental breakfast) TG (7.07 mg / dl (3h) and 2.45 mg / dl (6h)); VLDL (1.41 mg / dl (3h) and 0.49 mg / dl (6h)). On the con- trary, a decrease in LDL, ColT and HDL was observed after 3 hours, with rise of them after 6 hours of breakfast. With a difference in the average between LDL breakfasts (10.30 mg / dl (3h) and 11.56 mg / dl (6h)); ColT (7.78 mg / dl (3h) and 10.26 mg / dl (6h)); HDL (0.08 mg / dl (3h) and 0.97 mg / dl (6h)). Particularly the No HDL shows a constant be- havior in the 3 hours and then rise to 6 hours, with an av- erage difference between breakfast of 10.71 mg / dl (3h) and 12.71 mg / dl (6h). No significant difference was ob- served in the area under the curve (AUC) of any of the lipid profile variables between the two groups.

Table 3. Anthropometric and laboratory variables according to sex at the beginning of the study.

	Units	Experimental Breakfast		Usual Breakfast	
		Men	Women	Men	Women
n		14	14	13	23
Age	**Years**	21,8 +/- 2,9	21,7 +/- 3,3	21,6 +/- 4	20,2 +/- 1,8
Weight	**kg**	66,7 +/- 6,2	58,2 +/- 8,2	70,2 +/- 11,8	55,95 +/- 7,8
Size	**m**	1,75 +/- 0,4	1,59 +/- 0,05	1,75 +/- 0,06	1,59 +/- 0,5
BMI	**kg/m^2**	21,8 +/- 2,1	22,8 +/- 2,9	22,8 +/- 3,4	21,9 +/- 3,3
Fat	**%**	17,2 +/- 3,7	30,2. +/- 2,5	19,7 +/- 4,1	29,4 +/- 4,4
WHR		1,3 +/- 0,3	0,72 +/- 0,12	1,14 +/- 0,31	0,69 +/- 0,11
cTotal	**mg/dl**	155,05 +/- 15,5	173,3 +/- 27,01	172,9 +/- 16,03	172,3 +/- 18,7
cHDL	**mg/dl**	45,5 +/- 8,5	53,4 +/- 11,9	44,7 +/- 8,8	52,8 +/- 10,6
cLDL	**mg/dl**	93,9 +/- 19,9	105,4 +/- 28,6	114,6 +/- 24,5	107,2 +/- 21,5
cVLDL	**mg/dl**	17,1 +/- 4,05	14,8 +/- 6,2	18,3 +/- 3,9	14,7 +/- 3,8
cNoHDL	**mg/dl**	105,7 +/- 20	118,3 +/- 24,1	131,8 +/- 20,2	117,6 +/- 21,9
Tg	**mg/dl**	85,6 +/- 20, 2	74,1 +/- 31,2	91,7 +/- 19,6	73,8 +/- 19

BMI - Body mass index; WHR -waist / hip ratio.

Figure 1. It shows the behavior over time of each one of the lipid profile variables for both breakfasts.



In the correlation matrix, an inverse relationship was found between BMI and HDL (p = 0.049) and its respective AUC (p = 0.048), while the relationship was direct with total cholesterol (p = 0.009), LDL (p = 0.005), NoHDL (p = 0.005) and their respective AUC (p = 0.003), (p = 0.008), (P = 0.002). Likewise, the waist / hip index showed an inverse relationship with HDL (p = 0.012) and its AUC (p = 0.025) and a direct relation with fasting total cholesterol (p = 0.029). The percentage of fat had a direct relationship with fasting total cholesterol (p = 0.007) and its AUC (p = 0.02).

DISCUSSION

The results obtained in the study showed the change in time in each of the variables, especially in the TG. There was no significant difference between breakfasts in relation to the levels of the different components of the lipid profile. However, in the group that consumed the experimental breakfast there was a slight tendency to decrease circulating lipids (TG, VLDL, LDL, Non HDL, ColT) except HDL, as expected. This result may be due to the type of products used for the design of the diet, since the experimental breakfast, although it had complex carbohydrates, high PUFA and low SAFA, had less MUFA, important fatty acids in a healthy diet. The omega 3 fatty acids were not taken into account as well as Song *et al* [13]. Song and collaborators who in a study with 16 people compared 8 people with hypertriglyceridemia and 8 healthy people, with an average age of 53 and 46 years respectively, to whom one of two diets was applied, both with a PUFA / MUFA / SAFA ratio 1/1/1 but with different composition of fatty acids, one with high omega 3 and the other with low omega 3; found that in healthy people, TG had a maximum peak at 4 hours and a return to baseline at 8 hours, with an area under the incremental curve for lower TG in diets with omega 3 fatty acids, however, in the present study was car- ried out in young people, with an average age of 21 years, and with a much larger sample.

The polyphenol levels, which are important, were not taken into account in the study, since they influence the metabolism of the postprandial lipids, as they showed Annuzzi *et al*[14]. These authors evaluated, in people with signs of the metabolic syndrome, the response to different diets with omega 3 fatty acids and polyphenols. The authors found a significant decrease in the AUC of triglycerides and VLDL with diets rich in polyphenols. They also found that the isolated effect of them, by itself, was statistically significant. However, this was an 8-week intervention and did not evaluate the acute effect of them.

Few studies have evaluated the postprandial change in healthy people. In this study, samples were taken on fasting, at the third hour and at the sixth hour, as Sierra *et al* did[3] in a study in Colombia. They described that, in healthy people, it is in the third hour when the maximum triglyceride peak occurs and in the sixth hour it returns to its basal level. However, they did not take into account the behavior over time of the other components of the lipid profile.

The results obtained for triglyceride transporting lipoproteins (TG and VLDL) and total Cholesterol lipoproteins (LDL, HDL and ColT) were opposite. This could be because triglycerides are lipids of the exogenous diet and the first ones to be metabolized in the organism, after the metabolism of the chylomicrons, so they increase rapidly in the first three hours[15]. The lipoproteins cholesterol transporters, triglycerides and phospholipids, are manufactured mainly in the liver, from the proteins apoA and apoB in a second memento. These apoproteins have the function of carrying each of these lipids to be processed in the tissues in which they are metabolically active. Its subfractions have the ability to transport them differentially. This is how HDL3 are dense particles that are enriched with free cholesterol and phospholipids, while HDL2, which are less dense and relatively rich in proteins, are enriched with cholesterol esters and small amounts of triglycerides[16,17]. In the present study no quantifications of subfractions were made, which may be desirable in a future study.

The area under the curve evaluated the behavior over time of the different components of the lipid profile and no significant changes were found between breakfasts. A simi- lar result was reported by Días *et al*[18] who bought the acute effect of a diet rich in saturated fats and a diet rich in omega-6 polyunsaturated fatty acids. These investigators did not observe significant differences in the iAUC (area un- der the incremental curve) for plasma TG, total cholesterol, LDL or HDL. From the statistical analysis of bivariate corre- lations, it was found that both the BMI and the waist / hip index presented an inverse relationship with the fasting HDL. There was also a direct relationship between BMI and LDL, total cholesterol and Non-HDL. This indicates that a greater proportion of fat accumulated at the abdominal level, and the excessive consumption of carbohydrates and fats can reduce the production of HDL, since these transport lipids from the peripheral tissues to be metabolized by the liver. It also increases LDL, which are lipoproteins necessary to transport cholesterol to peripheral tissues[9]. Additionally, in this way, the direct relationship of fat percentage and hip waist index with fasting total cholesterol is explained. Similar results found by Navarrete *et al*[19] who described in a study with 3016 young participants, a direct association of BMI with cholesterol and triglycerides, as well as an inverse relationship with HDL levels, all statistically significant.

In the present study, there was no discrimination between smokers and non-smokers, which could be a factor of error for the study, since Sierra *et al*[20] demonstrated that the AUC of triglycerides was 21% higher in smokers, this could be key to explain our results.

This study has some limitations, this is how non-significant results can also be explained by the non-discrimination between athletes and sedentary people. The previous feeding of the members of each group was not evaluated either, since the postprandial metabolism usually adapts to the lifestyle and to the lipid load received daily[9]. Another important factor is the kind of food used in breakfasts, as these not only con- tain carbohydrates or fats, but also different concentrations of proteins and polyphenols, which interact in the postprandial metabolism[14]. There are also no known studies of the genetics of our population, which can also be a factor of confusion that influences the results found. On the other hand, the strengths of this study have to do with strict supervision and the rigor with which the study protocol was carried out. Additionally, the number of patients achieved an adequate adherence, with a loss of only 2% of the participants.

CONCLUSIONS

It was not possible to demonstrate that a diet rich in complex carbohydrates and mono and polyunsaturated fats reduced postprandial lipemia acutely compared to a diet high in saturated fatty acids and simple carbohydrates. Additional studies evaluating diets rich in these components are needed not only acutely but with a strict follow-up over time, as it would be expected that there would be a significant decrease in long-term interventions with a larger sample size.

ACKNOWLEDGMENT

Thanks to Universidad de Caldas for their financial support, to the volunteers who participated in the study and to Professor Carmen Dussán Luberth for her advice in the area of statistics.

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CAPITULO III: Alternative Foods in Cardio-Healthy Dietary Models That Improve Postprandial Lipemia and Insulinemia in Obese People

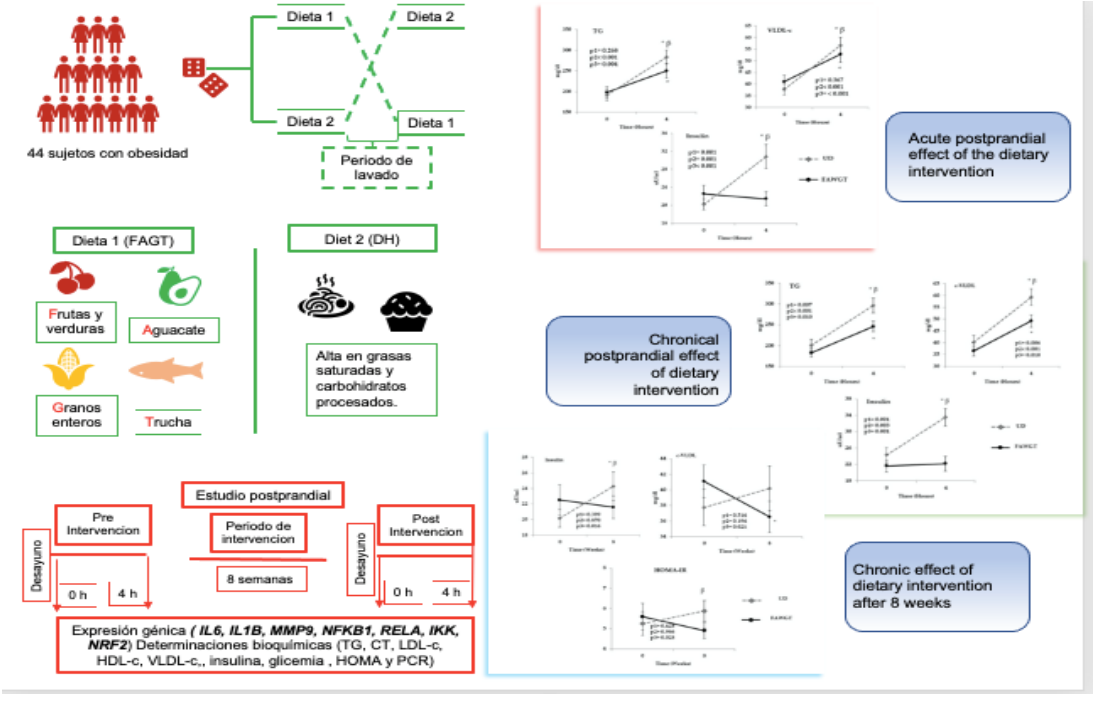
Capitulo III: Alternative Foods in Cardio-Healthy Dietary Models That Improve Postprandial Lipemia and Insulinemia in Obese People

Artículo de investigación publicado en Nutrients *2021*, *13*, 2225. https://doi.org/10.3390/nu13072225

Disponible online en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8308459/

Recibido: mayo 12 de 2021 Aceptado: junio 23 de 2021 Publicado: junio 29 de 2021

Indexada en Q1 según SJR y en A1 según Publindex.



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Alternative Foods in Cardio-Healthy Dietary Models That Improve Postprandial Lipemia and Insulinemia in Obese People

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Citation: Muñoz-Perez, D.M.; Gonzalez-Correa, C.H.; Astudillo-Muñoz, E.Y.; Porras-Hurtado, G.L.; Sanchez-Giraldo, M.; Lopez-Miranda, J.; Camargo, A.; Rangel-Zuñiga, O.A. Alternative Foods in Cardio-Healthy Dietary Models That Improve Postprandial Lipemia and Insulinemia in Obese People. *Nutrients* **2021**, *13*, 2225. https://doi.org/10.3390/nu13072225

Academic Editor: Queenie Chan

Received: 12 May 2021
Accepted: 23 June 2021
Published: 29 June 2021

Abstract: Obesity is one of the major health problems worldwide. Following healthy dietary patterns can be difficult in some countries due to the lack of availability of certain foods; thus, alternative foods are needed. Our aim was to evaluate the effect of a dietary pattern consisting of fruit, avocado, whole grains, and trout (FAWGT) on postprandial insulinemia and lipemia in obese Colombian subjects. A randomized controlled crossover study was conducted, in which 44 subjects with BMI ≥ 30 kg/m^2 followed either a FAWGT diet or a diet high in saturated fat and rich in processed carbohydrates. Levels of lipids and carbohydrates were measured during the postprandial state. The FAWGT diet reduced fasting insulin, VLDL, and HOMA-IR after 8 weeks ($p < 0.05$), while there was a lower postprandial increase in TG, VLDL, and insulin levels after both acute and chronic intake of FAWGT diet ($p < 0.05$). The intake of FAWGT-diet was characterized by high consumption of foods rich in fiber, MUFAs, and vitamins C and E ($p < 0.05$). The consumption of a diet composed of fruit, avocado, whole grains, and trout has emerged as a valid alternative to the foods included in other heart-healthy diets since it improves postprandial lipemia and insulinemia in obese people and has similar beneficial effects to these healthy models.

Keywords: obesity; postprandial lipemia; postprandial insulinemia; avocado; trout; alternative foods; healthy nutrients

1. Introduction

Overweight and obesity constitute a major health problem in the world [1]. In fact, the World Health Organization (WHO) declared obesity a pandemic after it was reported in 2016 that 39% of the adult population over 18 years old were overweight and 13% were obese [2]. This increased interest in the higher incidence of obesity has arisen because it is

the main cause of non-communicable diseases such as type 2 diabetes mellitus, cardiovascular diseases, and some types of cancer, which in turn increase the mortality rate due to these diseases and generate a heavy economic burden on health systems worldwide [3,4]. Obesity involves a complex interaction between genetic and environmental factors, including diet [5–7]. The adoption of unhealthy lifestyles and the adherence to a typical Western dietary model, including a low level of physical activity, and the consumption of saturated fats, carbohydrates, and sugary beverages, constitutes the main cause of obesity [8].

In addition, one of the main conditions that influences the development of obesity is the postprandial state, the period from the intake of food to its metabolism, in which there is a continuous fluctuation in the degree of lipemia and glycemia. There is a rapid remodeling of the lipoproteins and a greater number of metabolic adaptations compared to the fasting state [9]. The problem arises because in modern life, people often consume foods more than three times a day, so they remain in the postprandial state for most of the day [5,10], without the opportunity to achieve lipid clearance or glucose homeostasis.

In southern European countries on the Mediterranean coast, a healthy dietary model based on the consumption of olive oil, nuts, vegetables, and fish has been followed for thousands of years. Interventions with the Mediterranean Diet (Med diet) have shown a decrease in triglyceride-rich lipoproteins (TRL) in the postprandial state, with higher triglyceridemia after consumption of a meal rich in monounsaturated fatty acids (MUFA). However, this dietary model is characterized by a rapid clearing of triglyceride levels and a decrease in total cholesterol, LDL cholesterol, and TC/HDL-c ratio in the fasting state [10,11]. Furthermore, studies in Nordic countries show that a healthy Nordic diet lowers LDL cholesterol levels and blood pressure, among other healthy diets [12]. Thus, the beneficial effects of both Mediterranean and Nordic diets have been widely demonstrated [12–14]. However, the adoption of these healthy dietary models entails great difficulty in many countries of the world, mainly due to the unavailability or high cost of important foods such as olive oil, red wine, or salmon, among others. This suggests the need to find alternative models that include foods that are local, accessible, and economical in each region and have similar beneficial effects to those observed with other healthy models.

In the Colombian coffee region (Risaralda, Quindío, and Caldas departments), there is a wide variety of fruit and vegetables with cardio-protective potential due to their anti-inflammatory and antioxidant properties [15]. In fact, previous studies have shown a decrease in IL6, CRP, and leptin levels in obese women after 8 weeks of the intake of a diet high in monounsaturated fatty acids and rich in fruit and vegetables typical of the Colombian coffee region [15].

Based on the above, our aim was to evaluate the effect of the consumption of alternative foods such as fruit, avocado, whole grains, and trout, which contain healthy nutrients similar to the specific original foods from Med and Nordic diets, as alternative foods to those included in other healthy models. Additionally, we evaluated the effect of a dietary pattern consisting of fruit, avocado, whole grains, and trout on postprandial insulinemia and lipemia in obese Colombians.

2. Materials and Methods

Subjects

The present study included obese subjects between 45 and 60 years old, with a body mass index (BMI) ≥30 kg/m^2, without diagnosis of kidney, liver, thyroid, or di- agnosed cardiovascular disease but including hypertensive and dyslipidemic patients. Non-smokers, non-regular alcohol consumers, and patients not participating in weight reduction programs were also included. The primary endpoint was the postprandial triglyceride response. Based on previous studies, 35 individuals had to be included to detect a 15% difference in triglyceride response between the two interventions with 0.05 significance level and 80% power (type II error Z 0.2), assuming a 10% drop-out rate [16]. The recruitment of participants was performed between October 2017 and June 2018, with

1185 clinical records of patients diagnosed with obesity evaluated. After recruitment, 51 people were included in the study, 7 of whom had hypertension and 23 some kind of dyslipidemia. During the dietary intervention, 7 subjects dropped out for personal reasons unrelated to the study, while 44 subjects finished the study (Supplementary Figure S1). The study was carried out at the "Clínica Comfamiliar" located in Pereira, Colombia. All the participants signed an informed consent form before starting the study and were advised to continue their usual physical activity and lifestyle habits. The study protocol was approved by the Ethics Committee of the University of Caldas (University of Caldas registration number: 0406716) and the Clínica Comfamiliar Pereira, in accordance with the Declaration of Helsinki and is registered in ClinicalTrials.gov (NTC04920409).

Study Design

A randomized controlled crossover study was conducted. Volunteers followed two dietary models for 8 weeks each, including a 2-week washout diet between them. The order in which they started the interventions was randomized following a computerized assignment list using Excel software (Microsoft Office 2015, Excel 2013) (Figure 1). The diets followed during the intervention periods were: (1) a diet consisting mainly of the consumption of fruit, avocado and other vegetables, whole grains, and trout typical of the Colombian coffee region (FAWGT) (experimental diet); and (2) the usual diet consumed by the participants in their normal lifestyle (UD).

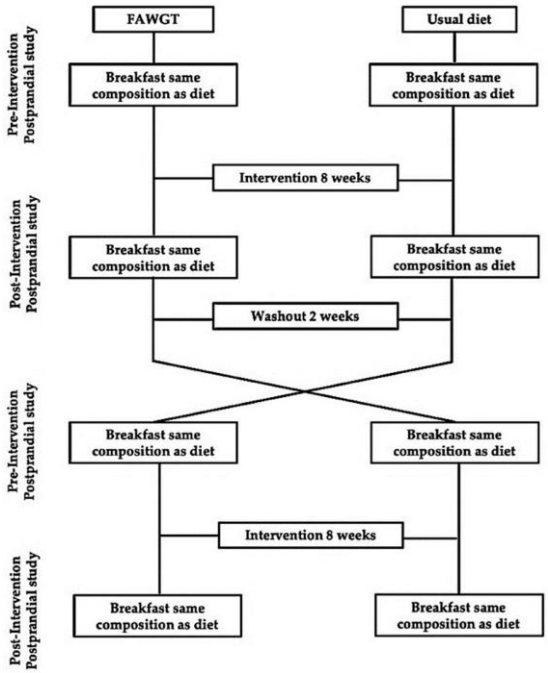

Figure 1. Study design. FAWGT, diet consisting of fruit, avocado, whole grains, and trout.

Diet Composition

Usual Diet (UD)

The usual diet consisted of 16% protein, 54% carbohydrates (CH), and 30% fat, of which 15% was saturated fat (SFA), 10% monounsaturated fat (MUFA), and 5% polyunsaturated fat (PUFA) in relation to the total caloric content (TCC). The usual diet was based on the food that the participants usually consumed prior to the study in their normal lifestyle. The determination of the composition of the usual diet was carried out through three 24-h recalls (2 non-consecutive weekdays and one weekend day) before beginning the study.

Washout Diet

The washout diet consisted of returning to the usual diet, characterized by a low consumption of fruit and vegetables < or equal to 2 servings per day, and no consumption of fish or whole grains. The macronutrient distribution remained the same.

Diet Composed of Fruit, Avocado, Whole Grains, and Trout (FAWGT)

The FAWGT diet was composed of 15% protein, 55% CH, and 30% fat, of which <10% was SFA, 14% MUFA, and 6% PUFA in the overall TCC. The FAWGT diet was designed based on foods with antioxidant and anti-inflammatory properties available in the Colombian coffee region, such as fruit and vegetables, trout, and whole grains. The macronutrient content corresponded with the Recommended Energy and Nutrient Intakes (RENIs) for the Colombian population; proteins 14–20%, total fat 20–35%, and carbohydrates 50–65% [17].

In the FAWGT diet, special emphasis was placed on the consumption of fruit and vegetables, legumes, whole grains, canola oil, and fish. To ensure adherence, some food available in the region was provided, including fish (trout), wholegrain cereals (traditionally wholegrain *arepas*—cornmeal pancakes), fats (avocado), and typical fruit from that region (e.g., *granadilla*, *chontaduro*, *uchuvas*, or *carambolo*). In the usual diet, the participants were not given any food but were instructed to eat the foods consumed in their usual diet in their normal lifestyle. The main difference between the diets was the quantity of dietary fiber, and the quality of the fat, carbohydrates, and proteins. A tolerable loss or gain of 1.5 kg of weight was estimated during the study. The food composition of the diets is summarized in Supplementary Table S1.

At the beginning of the dietary intervention period, each participant was given an individualized food guide containing the suggested food group and portions, with a wide variety of foods allowed for greater adherence to the diet. In addition, specific times for consumption of the foods and precise instructions for the dietary intervention were given. In addition, the subjects were given a talk advising them how to quantify the portions, which would later be converted into grams according to the procedure described by Astudillo et al., 2019 [15]. The food portions were standardized with all the participants using synthetic models, adapted according to the Colombian nutritional guidelines [18], so that they could provide a more accurate report of the portions consumed during the intervention.

The Nutritionist Pro software version 7.4.0 (Axxya Systems, Woodinville, WA, USA) was used to calculate energy, macro, and micronutrients. This software includes world food information (USA, Europe, Asia, Central America), and when certain types of Colombian food were not included in the software they were added based on the values provided by Colombian nutritional guides [18].

Postprandial Study

An analysis was carried out at the level of the acute postprandial response, which is defined as the effect from breakfast until 4 h later without a previous period of dietary intervention. A further analysis was carried out of the chronic postprandial response, which is defined as the effect from breakfast until 4 h later after a dietary intervention period of 8 weeks.

The postprandial studies were carried out at the beginning of the study (pre-intervention) and then after 8 weeks of dietary intervention (post-intervention) (Figure 1). The participants were given an appointment at the health center at 7.00 am, after at least 12 h of fasting and a 5-day abstinence from alcohol. They consumed a breakfast based on the same composition of the diet in which they were randomized for the dietary intervention period. The composition of the breakfasts for the postprandial study is shown in Supplementary Table S2. The blood samples were obtained by venipuncture at baseline and 4 h after breakfast. During the postprandial period, the participants did not consume any more food, although they were allowed to drink water. The breakfasts were composed of the following foods. FAWGT diet:

whole-grain *arepa* (with unrefined corn flour), cheese, oats, granadilla, mango, linseed, nuts, almonds, peanuts, and yogurt. Usual diet: egg, cheese, butter, whole milk, traditional white *arepa* (with refined corn flour), traditional *buñuelo* (made from wheat flour with cheese), coffee, and sugar.

Nutritional Follow-Up of the Dietary Intervention

Before starting the dietary intervention period (pre-intervention), at the midpoint of the study (week 4) and at the end (week 8), all the participants completed three 24-h recalls (2 non-consecutive weekdays and one weekend day) to obtain information about food, ingredients, and preparations consumed in standard units of measurement (grams). In addition, a weekly telephone call was made to answer any questions relating to the diet (recipes, menu, and quantities) and to motivate adherence to the assigned dietary model. Moreover, in week four of each intervention, the participants attended the hospital for an interview with the main researcher in order to take anthropometric measurements, evaluate the follow-up of the dietary instructions, and answer any questions that may have arisen during the intervention, as well as motivating them to continue with the study. To collect the information on food consumption, formats and questionnaires previously published by the research group were used [15]. The protocol to establish adherence to the diet was the three 24-h recalls reminder food record (2 non-consecutive weekdays and one weekend day), which was carried out 5 times during each intervention period: weeks 4, 8, 10, 14, and 18.

Biochemical Measurements of Metabolic Parameters

Venous blood from the participants was collected in tubes containing EDTA after a 12-h overnight fast, and these were placed in containers with ice and kept in the dark. Samples were collected at baseline and 4 h after breakfast, both in the pre-intervention stage and in the post-intervention stages. Immediately after the blood extraction, the plasma was separated by centrifugation at 1500× *g* for 15 min at 4 °C. The plasma samples were aliquoted and stored at —80 °C until the measurements were made, to avoid inter-assay variations.

Lipid variables were assessed using a COBAS Hitachi autoanalyzer using specific reagents (Roche, Basel, Switzerland). The levels of total cholesterol (TC) and triglycerides were measured by colorimetric enzymatic methods, high-density lipoprotein (HDL-c) was measured by colorimetric assay, and low-density lipoprotein (LDL-c) concentration was calculated by the Friedewald equation, using the following formula: LDL-c = TC— (HDL-c + TG/5) [19]. VLDL particles were calculated by the following formula: TG/5. Glucose measurements were performed by the hexokinase method using Roche Diagnostics reagents. Plasma insulin concentrations were measured on a Roche COBAS 6000 system (Roche, Basel, Switzerland). The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was calculated was calculated using the following formula HOMA-IR = Fasting insulinemia (μU/mL) * Fasting glycemia (mg/dL)/405 [20].

Statistical Analysis

All the data are expressed as mean values and standard error. SPSS 20 for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The differences in the baseline characteristics of subjects included in the study were evaluated by a ONE-WAY ANOVA test. The differences between the baseline and the post-intervention period were analyzed using analysis of variance (ANOVA) for repeated measures. The Greenhouse-Geisser contrast statistic was used when the sphericity assumption was not satisfied. In this analysis, we studied the overall diet influence (global ANOVA, p for diet influence), the kinetics of the postprandial response (p for time), and the interaction of the two factors (diet vs. time). When post hoc test analyses were pertinent, we used multiple comparison tests with the Bonferroni correction. $p < 0.05$ was considered as statistically significant.

Results

Baseline Characteristics of Subjects Included in the Study

Table 1 shows the anthropometric and biochemical characteristics of the study participants before any dietary intervention at baseline. In addition, Table 2 shows the characteristics of the participants before starting each dietary intervention after the wash-out period. We observed no significant differences in the clinical and anthropometric characteristics, except for levels of HDL cholesterol, which were lower in the group of patients assigned to the FAWGT diet compared with the patients assigned to the usual diet ($p < 0.001$) (Table 2).

Table 1. Baseline characteristics of the patients included in the study before any dietary intervention.

	Total *n* = 44	**Women *n* = 34**	**Men *n* = 10**
Age	50.8 ± 6.3	50.5 ± 6.5	51.9 ± 5.5
Weight (kg)	88.6 ± 13.5	87.0 ± 13.7	94.4 ± 11.5
Waist-hip ratio	0.91 ± 0.1	0.89 ± 0.1	0.97 ± 0.1
Body mass index (kg/m^2)	35.6 ± 4.2	36.2 ± 4.3	33.7 ± 3.3
Fat (%)	42.3 ± 4.2	43.6 ± 2.7	37.9 ± 5.7
Systolic blood pressure (mmHg)	122.7 ± 13.4	121.0 ± 12.3	128.7 ± 16.1
Diastolic blood pressure (mmHg)	81.1 ± 9.0	79.5 ± 8.4	86.6 ± 9.2
Handgrip strength (kg)	26.6 ± 7.7	24.6 ± 5.7	33.7 ± 9.8
Insulin (μU/mL)	20.8 ± 14.0	18.6 ± 7.3	28.15 ± 25.83
Glucose (mg/dL)	95.1 ± 11.1	93.9 ± 9.5	99.1 ± 15.2
HOMA-IR	5.0 ± 3.9	4.4 ± 1.9	7.3 ± 7.2
TC (mg/dL)	203.5 ± 37.4	203.4 ± 38.8	203.9 ± 34.2
HDL-c (mg/dL)	43.1 ± 10.5	44.1 ± 11.2	39.7 ± 6.6
Non- HDL-c (mg/dL)	160.4 ± 38.8	159.2 ± 41.1	164.2 ± 31.0
LDL-c (mg/dL)	122.2 ± 35.4	121.7 ± 36.8	124.1 ± 32.1
VLDL-c (mg/dL)	38.2 ± 18.1	37.6 ± 16.4	40.1 ± 24.0
TG (mg/dL)	190.8 ± 90.4	187.9 ± 81.8	200.4 ± 120.0
hs-CRP (mg/L)	5.1 ± 5.1	5.8 ± 5.6	2.8 ± 1.2

Data shows the mean ±SD. HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; TC: total cholesterol; HDL-c: high-density lipoproteins; LDL-c: low-density lipoproteins; VLDL-c: very low-density lipoproteins; TG: triglycerides; hs-CRP: C-reactive protein.

Table 2. Characteristics of the participants before starting each dietary intervention after the wash-out period.

	FAWGT	**UD**	***p* Value**
N	44	44	n.a.
Weight (kg)	88.5 ± 13.5	88.3 ± 13.7	0.322
Waist-hip ratio	0.90 ± 0.1	0.91 ± 0.1	0.128
Body mass index (kg/m^2)	35.7 ± 4.3	35.5 ± 4.3	0.206
Fat (%)	42.7 ± 3.5	42.4 ± 4.5	0.341
Systolic blood pressure (mmHg)	122.1 ± 11.7	120.1 ± 12.6	0.343
Diastolic blood pressure (mmHg)	78.6 ± 9.3	80.1 ± 8.0	0.224
Handgrip strength (kg)	26.9 ± 7.3	27.7 ± 8.2	0.261
Insulin (μU/mL)	22.5 ± 13.0	20.2 ± 7.8	0.239
Glucose (mg/dL)	94.3 ± 10.9	95.9 ± 11.0	0.221
HOMA-IR	5.6 ± 3.7	5.3 ± 2.3	0.591
TC (mg/dL)	201.3 ± 36.5	202.0 ± 35.3	0.811
HDL-c (mg/dL)	40.1 ± 9.9	43.4 ± 10.7	<0.001
Non- HDL c (mg/dL)	161.0 ± 38.2	159.2 ± 36.4	0.572
LDL-c (mg/dL)	118.4 ± 36.1	118.0 ± 34.3	0.922
VLDL-c (mg/dL)	41.1 ± 18.4	37.7 ± 15.5	0.218
TG (mg/dL)	198.2 ± 88.8	191.2 ± 86.3	0.811
hs-CRP (mg/L)	4.3 ± 2.5	4.6 ± 2.4	0.248

Data shows the mean ±SD. FAWGT: diet composed of fruit, avocado, whole grains, and trout; UD: usual diet. HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; TC: total cholesterol; HDL-c: high-density lipoproteins; LDL-c: low-density lipoproteins; VLDL-c: very low-density lipoproteins; TG: triglycerides; hs-CRP: C-reactive protein.

Energy Consumption and Dietary Composition after the Intervention Periods

The analysis of energy consumption and dietary composition after 8 weeks with the both interventions (FAWGT and UD) showed an increase in the intake of fiber, MUFA, Omega-3 FA, beta-carotenes, vitamin C, and vitamin E by the consumption of FAWGT diet compared with the UD. In contrast, we observed a lower intake of SFA, Omega-6/Omega-3 ratio, cholesterol, Zn, and Se after 8 weeks of intervention with the FAWGT diet than the UD, all $p < 0.05$ (Table 3).

Table 3. Dietary composition at baseline and after 8 weeks of intervention.

	FAWGT		UD				
	0 Week	**8 Week**	**0 Week**	**8 Week**	***p* Diet**	***p* Time**	***p* Interaction**
Energy (Kcal)	1774.2 ± 265.5	1627.9 ± 152.9 (a)	1900.2 ± 216.7	1800.6 ± 204.7 (a) (b)	<0.001	<0.001	0.374
Protein (E%)	16.6 ± 2.3	16.7 ± 2.5	16.5 ± 2.6	17.2 ± 1.7	0.492	0.212	0.337
Carbohydrates (E%)	50.8 ± 5.1	53.6 ± 4.7 (a)	53.7 ± 4.4	53.8 ± 3.9	0.012	0.030	0.054
Total Fiber (g)	13.6 ± 4.1	32.9 ± 5.8 (a)	14.4 ± 4.4	14.6 ± 3.9 (b)	<0.001	<0.001	**<0.001**
Total Fat (E%)	30.6 ± 6.4	29.3 ± 3.8	29.7 ± 3.6	29.0 ± 3.1	0.339	0.072	0.673
SFA (E%)	10.1 ± 2.3	7.4 ± 1.5 (a)	10.8 ± 2.1	10.6 ± 1.6 (b)	<0.001	<0.001	**<0.001**
MUFA (E%)	10.8 ± 2.2	12.1 ± 1.9 (a)	9.2 ± 1.6	9.1 ± 1.5 (b)	<0.001	0.018	**0.011**
PUFA E (%)	6.9 ± 2.5	6.7 ± 1.4	4.9 ± 1.1	4.7 ± 1.1 (b)	<0.001	0.448	0.956
Linoleic acid (g)	11.6 ± 4.4	9.8 ± 1.8 (a)	8.5 ± 2.4	8.1 ± 3.1 (b)	<0.001	0.019	0.166
Alpha-linolenic acid (g)	1.0 ± 0.4	1.6 ± 0.7 (a)	0.9 ± 0.3	0.8 ± 0.3 (b)	<0.001	0.019	**<0.001**
W6/W3 ratio	11.9 ± 2.8	7.0 ± 3.0 (a)	10.0 ± 1.8	11.0 ± 6.2 (b)	0.062	0.003	**<0.001**
Cholesterol (mg)	302.3 ± 136.2	242.9 ± 83.0 (a)	322.9 ± 139.0	333.3 ± 117.0 (b)	<0.001	0.151	**0.023**
Beta-carotene (✪g)	1918.1±1307.6	6436.3 ± 2806.6 (a)	1790.1 ± 1121.4	1788.4 ± 1021.2 (b)	<0.001	<0.001	**<0.01**
Vitamin C (mg)	91.5 ± 66.8	207.1 ± 57.8 (a)	108.7 ± 65.7	92.2 ± 41.4 (b)	<0.001	<0.001	**<0.001**
Vitamin E (mg)	4.4 ± 1.6	7.0 ± 1.7 (a)	3.9 ± 1.1	3.6 ± 0.9 (b)	<0.001	<0.001	**<0.001**
Folate (✪g)	270.4 ± 101.8	305.8 ± 69.7 (a)	272.6 ± 90.7	285.2 ± 86.7	0.321	0.037	0.441
Mg (mg)	206.0 ± 48.5	294.4 ± 50.2 (a)	227.3 ± 47.1	220.8 ± 38.3 (b)	0.321	0.037	0.441
Zn (mg)	8.6 ± 2.6	7.2 ± 1.2 (a)	8.1 ± 3.3	8.8 ± 2.5 (b)	0.042	0.340	**0.001**
Se (✪g)	77.0 ± 20.4	63.4 ± 13.5 (a)	79.2 ± 22.5	81.7 ± 20.8 (b)	<0.001	0.018	**0.002**

Values expressed as mean ±SD. FAWGT: diet composed of fruit, avocado, whole grains, and trout; UD: usual diet; SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; Mg: magnesium; Zn: zinc; Se: selenium. Variables were calculated using a repeated measurement analysis through SPSS (now PASW Statistic for Windows, version 21.0) (IBM, Chicago, IL, USA). In bold $p < 0.05$ in the interaction diets vs. time. (a) $p < 0.05$ relative to baseline values in the diet. (b) $p < 0.05$ between diets in the same time period.

Acute Postprandial Effect of the Dietary Intervention

The analysis of the acute postprandial effects of the intake of a diet rich in fruit, avocado, whole grains, and trout available in the Colombian coffee region (FAWGT) compared with a UD was carried out at the beginning of the study (Figure 1) and showed that the two models induced a postprandial increase in triglyceride and VLDL levels after 4 h compared to the fasting state (both diets $p < 0.001$). However, this postprandial increase was lower in both TG and VLDL levels ($p = 0.046$ and $p = 0.023$, respectively) after the acute intake of the FAWGT diet compared to the UD. Moreover, the acute intake of the UD induced a postprandial increase in insulin levels compared to the fasting state ($p < 0.001$). In fact, insulin levels were significantly higher at 4 h after the acute intake of the UD compared with the acute intake of the FAWGT diet ($p < 0.001$) (Figure 2). No significant differences between diets were observed in the other variables analyzed (glucose, total cholesterol, non-HDL-c, LDL-c, and CRP), except for the HDL-c plasma levels, which decreased after the acute consumption of both diets (Figure S2).

Chronical Postprandial Effect of Dietary Intervention

Further, we analyzed at the postprandial state the chronic effect of the consumption for 8 weeks of the FAWGT or the usual diet (chronic postprandial effect), which showed an increase at 4 h with respect to baseline in the levels of triglyceride and c-VLDL after the intake of the two diets (both $p < 0.001$). However, this increase was lower after the intake of the FAWGT diet than the UD, in both triglyceride and VLDL levels (both $p = 0.001$). Finally, after 8 weeks of dietary intervention, the usual diet induced an increase in insulin levels at 4 h after breakfast compared with baseline ($p = 0.002$). This increase was statistically significant between both diets at 4 h of the postprandial state ($p < 0.001$) (Figure 3). No significant differences between diets were observed in the other variables analyzed (blood

pressure, glucose, total cholesterol, HDL-c, non-HDL-c, and CRP), except for the LDL-c plasma levels, which were higher in FAWGT diet (Figure S3).

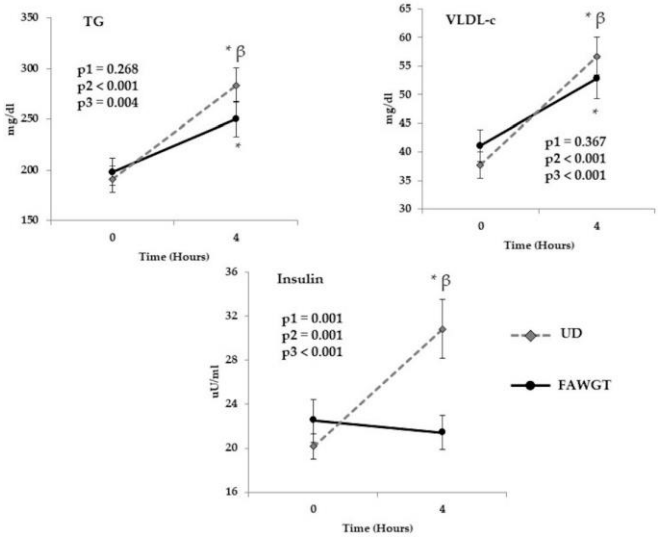

Figure 2. Acute postprandial effect of dietary intervention. Results correspond to the postprandial study performed on the first day of each dietary period. Values are shown as mean ± S.E.M, and the analysis corresponds to an ANOVA of repeated measurements, where p1 = diet influence; p2 = time, kinetics after 4 h; and p3 = the interaction of the two factors (diet vs. time). * $p < 0.05$ = 4 h after breakfast compared to fasting. = $p < 0.05$ FAWGT vs. UD. FAWGT: diet based on fruit, avocado, whole grains, and trout; UD: usual diet.; TG: triglycerides; VLDL-c; very low-density lipoproteins.

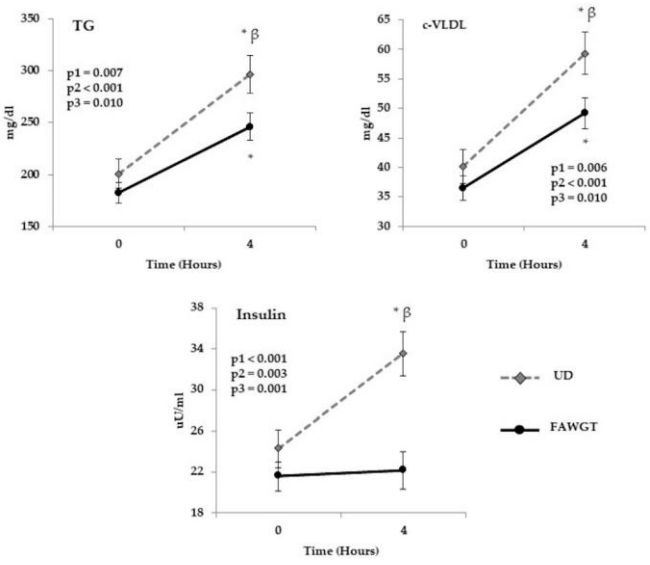

Figure 3. Chronic postprandial effect of dietary intervention. Results correspond to the postprandial study performed on the last day of each dietary period. Values are shown as mean ± S.E.M, and the analysis corresponds to an ANOVA of repeated measurements, where p1 = diet influence; p2 = time, kinetics after 4 h; and p3 = the interaction of the two factors (diet vs. time). * $p < 0.05$ = 4 h after breakfast compared to fasting. = $p < 0.05$ FAWGT vs. UD. FAWGT: diet based on fruit, avocado, whole grains, and trout; UD: usual diet.; TG: triglycerides; VLDL-c; very low-density lipoproteins.

Chronic Effect of Dietary Intervention after 8 Weeks

The analysis of the fasting status after 8 weeks of intervention showed that the usual diet (UD) increased the insulin levels after the intervention period compared to the baseline (p = 0.006). This difference was statistically significant compared with the FAWGT diet after 8 weeks of intervention (p = 0.018). Additionally, the FAWGT diet induced a decrease in VLDL levels after the intervention period compared to the baseline (p = 0.026). Insulin resistance, assessed by the HOMA-IR index, was lower after 8 weeks of the FAWGT diet than the UD (p = 0.013) (Figure 4). Moreover, we found a reduction on body weight after the FAWGT diet (p < 0.001), in parallel with decrease in BMI (p < 0.001), whereas we observed an increase in BMI after the UD period (p < 0.001). We also observed a decrease in HDL-c levels after the UD period (p = 0.039). No statistically significant differences were found in fat percentage, waist hip index, blood pressure, glucose, total cholesterol, non-c HDL-c, LDL-c, triglycerides, and C-reactive protein (Table S3).

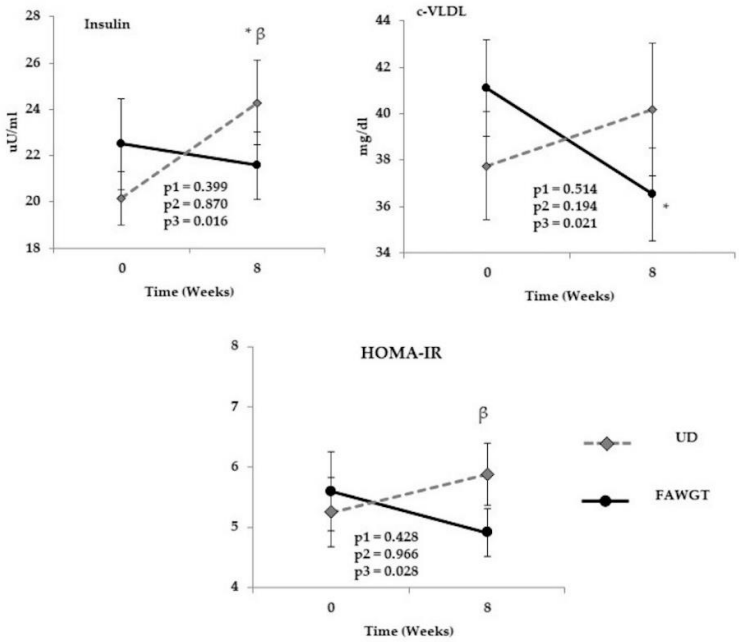

Figure 4. Chronic effect of the intake of a diet based on fruit, avocado, whole grains, and trout after 8 weeks of intervention. Values are shown as mean ± S.E.M, and the analysis corresponds to an ANOVA of repeated measurements, where p1 = diet influence; p2 = time, kinetics after the intervention period in fasting state; and p3 = the interaction of the two factors (diet vs. time). * p < 0.05 after 8 weeks of intervention compared to baseline. = p < 0.05 FAWGT vs. UD. HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; FAWGT: diet based on fruit, avocado, whole grains, and trout; UD: Usual diet.

Discussion

Our study shows that the intake of a diet composed by fruit, avocado, whole grains, and trout could emerge as a valid alternative to other healthy dietary patterns, as it led to an improvement in postprandial lipemia and insulinemia and a decrease in insulin resistance in obese people but without causing clinically significant weight loss. This was supported by the fact that consumption of an FAWGT diet increased the quantity of healthy fatty acids such as MUFA, Omega 3, and fiber, as well the quantity of molecules with antioxidant power, such as vitamins C and E. Additionally, the FAWGT diet reduced the increase in postprandial triglycerides (TG) and VLDL levels after both acute and chronic intake compared to the usual diet. Additionally, the intake of the FAWGT diet prevented an increase in postprandial insulin levels in both the acute and chronic intervention in contrast to the UD, without significant differences between diets in postprandial glucose increases

after both acute and chronic intake. Finally, these results were obtained in free-living conditions with food available in the region, without the use of any food supplements, which would allow us to generalize these findings.

Southern European countries on the coast of the Mediterranean Sea advise their populations to consume the Mediterranean diet, which is rich in extra virgin olive oil, fish, fruit, nuts, vegetables, and legumes [21]. Additionally, the Nordic diet recommends the frequent consumption of fruit, berries, vegetables, legumes, potatoes, whole grains, nuts, seeds, rye breads, fish, seafood, low-fat dairy, herbs, spices, and rapeseed (canola) oil [22]. Both of these dietary models help to prevent high blood pressure, lower cholesterol levels and obesity-associated low-grade chronic inflammation and reduce the risk of cardiovascular disease and type 2 diabetes mellitus. The diets are considered healthy dietary models and are based on common foods in these regions that are not always easily available in other countries. However, there is a need to implement dietary models with alternative foods with a similar nutrient content that have similar metabolic benefits in terms of glucose and lipids.

Previous studies have shown that the Mediterranean diet improves the lipid profile during the postprandial state [14,21]. In fact, it has been suggested that the consumption of the monounsaturated fatty acids (MUFA) present in olive oil decreases postprandial glucose and insulin concentrations after breakfast and increases HDL cholesterol (HDL-c) and glucagon-like pepide-1 (GLP-1) concentrations compared with a carbohydrate- rich diet [23]. GLP-1 decreases lipid and glucose levels by enhancing insulin secretion and synthesis and improves pancreatic -cell proliferation. Other studies show that this proliferation is progressive as the MUFA to SAFA ratio increases [23,24]. Other studies have shown that participants who ingest 20% of their energy as MUFA have an earlier increase and a faster clearance of postprandial plasma TG and large concentrations of triglyceride-rich lipoproteins (TRL-TG) compared with SFA and low-fat diets [25]. In our study, we observed a reduced increase in TG and VLDL in both acute and chronic postprandial state after the intake of the FAWGT diet model; in addition, there was a decrease in fasting VLDL after 8 weeks of intervention with the same diet. This effect could be attributable to the increase in MUFA intake from 10.8 to 12.1%, whose main source was avocado, with an intake of 18 g/d. These findings are consistent with those found by Anderson-Vasquez, HE et al., where the addition of 250 g avocado to the usual diet decreased the levels of total cholesterol, LDL-c and TG [26]. Similarly, our study showed an increase in omega-3 intake and a decrease in the omega-6/omega-3 ratio from 12:1 to 6:1, possibly due to the consumption of 280 g/week of trout. The replacement of olive oil by avocado and the consumption of trout could have similar effects on lipemia and postprandial insulinemia to those found with established healthy diets, considering that both are an important source of MUFA (55–83% and 63%, respectively).

In addition, one previous study demonstrated a postprandial decrease of insulin and triglycerides after replacing refined grains with whole grains to achieve a fiber consumption of 40 g/d, although this reduction was not parallel to the reduction of glucose [27]. Sun et al. found a decrease in postprandial insulin regardless of the degree of fatty acid saturation after the intake of a combination of 50 g carbohydrates (low and high glycemic index) and 40 g fat (SAFA, MUFA, and PUFA) [28]. In this context, the contribution of our study is to suggest that the consumption of *arepa* with whole-grain corn, brown rice, and oatmeal of 115 g/d increases the fiber intake. This was higher in the FAWGT (32 g/d) than the UD (15 g/d). This effect could be due to fiber being metabolized in the intestinal microbiota, whose products are short-chain fatty acids, especially butyrate and propionate, which could improve insulin sensitivity [29,30]. Moreover, this potentially favorable effect of the FAWGT diet could also reduce the cardiovascular risk by reducing insulin resistance, as recently described [31]. Similarly, this alternative dietary model was able to decrease the acute and chronic postprandial insulin response, which suggests an improved glucose metabolism, as evidenced by the HOMA-IR index. However, further research is needed to ascertain why no significant differences in glucose levels were observed.

Finally, fruit consumption is associated with an increase in antioxidant capacity, increasing the potential for the elimination of reactive oxygen species, which show high levels in obese people. Vitamin C and E decrease oxidative damage, inhibiting lipid peroxidation and maintaining pancreatic cell function, which may inhibit gluconeogenesis and glycogenolysis [32]. Likewise, vitamin C may increase the action of lipoprotein lipase in adipose tissue and decrease levels of TG, VLDL, and LDL cholesterol [33]. This study showed an increase in vitamin C and E levels from 91.2 to 207.13 mg and from 4.43 to 7.01 mg, respectively ($p < 0.001$). The main sources of these vitamins were the typical fruits of the Colombia coffee region, such as mango, orange, purple passion fruit, and *chontaduro*. FAWGT diet was based in the consumption of typical arepa, rice, oat, lentils, tomato, carrot, lettuce, onion, beans, avocado, trout, mango, orange, apple, pear, tangerine, pineapple, papaya, *chontaduro*, *uchuva*, *carambolo*, and *granadilla*, which altogether add fiber, antioxidant, vitamins, and MUFA in different proportions. Therefore, it is complex to discern which specific component is driving the differences found between FAWGT and the usual diet as several foods were introduced.

Our study has also other limitations. The sample size was low, although the experimental randomized crossover design allowed us to detect the effect of the intake of a diet composed by fruit, avocado, whole grains, and trout. However, this fact, together with the short duration of each dietary period, may limit the extrapolation of these findings, and therefore further studies would be needed to confirm them.

Conclusions

In conclusion, the consumption of a diet composed of fruit, avocado, vegetables, whole grains, and trout can be considered a valid alternative to other heart-healthy diets, since it improves postprandial lipemia and insulinemia in obese people without causing clinically significant weight loss and shows similar beneficial effects to these healthy models.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nu13072225/s1, Figure S1: Flow chart of study participants, Figure S2: Acute postprandial effect of dietary intervention on other biochemical variables, Figure S3: Chronic postprandial effect of dietary intervention on other biochemical variables, Table S1: Recommended foods in the study, Table S2: Composition and caloric distribution of the breakfasts used in the postprandial study, Table S3: Characteristics of subjects included in the study after and before the dietary intervention

Author Contributions: Conceptualization, D.M.M.-P. and C.H.G.-C.; Formal analysis, D.M.M.-P. and O.A.R.-Z.; Funding acquisition, D.M.M.-P.; Investigation, E.Y.A.-M. and G.L.P.-H.; Methodology, E.Y.A.-M., G.L.P.-H., and M.S.-G.; Resources, G.L.P.-H., J.L.-M., A.C., and O.A.R.-Z.; Supervision, C.H.G.-C., A.C., and O.A.R.-Z.; Validation, E.Y.A.-M.; Writing—original draft, D.M.M.-P.; Writing—review and editing, C.H.G.-C., A.C., and O.A.R.-Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by MINISTERIO DE CIENCIA, TECNOLOGIA E INNOVACION (COLCIENCIAS) from the Colombian government, grant number to D.M.M.P in the Call for National Doctorates 647 of 2014. This study was financed by the Universidad de Caldas through the "General call for the financing of Research, Innovation and Creation of the University of Caldas 2014" and the "General call for project financing of Research, research-creation and innovation 2016" and by the Universidad Libre de Pereira through the "Internal Call ULP 07 of 2017". Oriol Alberto Rangel Zuñiga and Antonio Camargo are supported by an ISCIII research contract (Programa Miguel-Servet CP19/00142 and CPII19/00007, respectively).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of UNIVERSITY OF CALDAS and CLINICAL COMFAMILIAR RISARALDA, Colombia (protocol code 0406716 approved by act 10 of 2015 from University of Caldas).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author and to the principal researchers of the project D.M.M.-P. and C.H.G.-C.

Acknowledgments: We would like to thank the PhD professors in Biomedical Sciences of the Colombian coffee region for their contributions. Our thanks also go to Andrés Morales for his contributions technicians in conducting the tests in Maimonides Institute Biomedical Research Department of Córdoba, Spain to Industrias Alimenticias Monserrat for supplying the dark chocolate to the participants, and to the Maimonides Institute Biomedical Research Department of Córdoba (IMIBIC) for making its entire infrastructure available to us.

Conflicts of Interest: The authors declare no conflict of interest.

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CAPITULO IV: Effect of the 8 weeks' consumption of a dietary pattern based on fruits, avocado, whole grains, and trout on postprandial inflammatory and oxidative stress gene-expression in obese people: a randomized controlled trial

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Artículo de investigación publicado en Nutrients *2023*

Disponible online en: https://www.mdpi.com/2072-6643/15/2/306

Recibido: 4 de octubre de 2022. Aceptado: 3 de enero de 2023. Publicado: 7 de enero de 2023

I**ndexada en Q1 según SJR y en A1 según Publindex para el año 2023**

nutrients

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Effect of 8-Week Consumption of a Dietary Pattern Based on Fruit, Avocado, Whole Grains, and Trout on Postprandial Inflammatory and Oxidative Stress Gene Expression in Obese People

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Citation: Muñoz-Pérez, D.M.; González-Correa, C.H.; Astudillo Muñoz, E.Y.; Sánchez-Giraldo, M.; Carmona-Hernández, J.C.; López-Miranda, J.; Camargo, A.; Rangel-Zúñiga, O.A. Effect of 8-Week Consumption of a Dietary Pattern Based on Fruit, Avocado, Whole Grains, and Trout on Postprandial Inflammatory and Oxidative Stress Gene Expression in Obese People. *Nutrients* **2023**, *15*, 306. https://doi.org/10.3390/nu15020306

Academic Editor: Hirofumi Tanaka

Received: 4 October 2022
Revised: 30 December 2022
Accepted: 3 January 2023
Published: 7 January 2023

Abstract: Overweight and obesity constitute a major global public health problem. Healthy dietary patterns induce changes at the molecular level. Currently, there are no studies evaluating the effect of a diet based on fruit, avocado, whole grains, and trout (FAWGT diet) on the expression of obesity-related genes. This randomized controlled crossover study included 44 obese Colombians with BMI ≥30 kg/m^2 who followed either a FAWGT diet or a usual diet (UD) characterized by a high intake of saturated fat and foods rich in processed carbohydrates. After 8 weeks of intervention, a postprandial expression study of inflammation and oxidative stress-related genes was carried out with a real-time PCR. The intervention with a FAWGT diet decreased the expression of inflammatory (*NFKB1*, *IL6*, *IL1β*) and oxidative stress (*NFE2L2*) genes compared with the intake of the UD. Finally, the postprandial expression of *NFkB1* was positively correlated with triglyceride levels after a dietary intervention with the FAWGT diet and the *IL1β* gene, and likewise with insulin levels after following the usual diet. The consumption of the FAWGT diet for 8 weeks reduced the inflammatory status; thus, it can be considered a valid alternative to other healthy diets, since it induces beneficial changes on the genes involved in inflammation and oxidative stress in obese people.

Keywords: gene expression; healthy diet; inflammation; obesity; oxidative stress

1. Introduction

The incidence of obesity in the world has tripled over the last 40 years, and overweight and obesity have now reached pandemic proportions and become a global health problem [1]. In 2016, over 1.9 billion adults were overweight, of whom over 650 million were obese [2]. Obesity is considered a starting point for the development of other diseases with

high mortality rates, such as cardiovascular disease, type 2 diabetes mellitus, and some cancers [3]. For this reason, efforts are being made to understand the mechanisms underlying overweight and obesity. Knowledge of these mechanisms allows us to plan effective actions to modulate patients' metabolism in order to keep their weight at healthy levels.

It has been proposed that a chronic low-grade inflammatory state, characterized by an increase in proinflammatory molecules, constitutes the link between obesity and chronic noncommunicable diseases such as obesity, and that the inflammation in obesity originates from dysfunctional adipose tissue due to the excess of nutrients. In this scenario, an infiltration of macrophages occurs, stimulating the expression of inflammatory genes such as the cytokines *IL1β* or *IL6* [4], which may be modulated by diet or specific nu- trients, possibly through the activation of signaling pathways or by acting directly on transcription factors [3,5]. For example, an intervention comparing the consumption of a Mediterranean-rich diet with a Western dietary pattern that is rich in saturated fatty acids showed a decrease in the expression of the proinflammatory genes *p65* and *MCP1* [6]. Additionally, after a breakfast rich in SFA, Monfort et al. [7] found an increase in *IL1β* expression compared to a breakfast rich in polyunsaturated fatty acids and fiber.

One of the main actions adopted to manage obesity is the adherence to healthy lifestyle habits, such as physical activity and healthy diets. The Mediterranean diet and the Nordic diet have been accepted as healthy dietary patterns; in fact, previous studies have shown that adherence to these patterns improves fatty acid metabolism and decreases insulin resistance [8]. In addition, the consumption of these dietary patterns has been associated with a decrease in the activation of obesity-associated processes such as inflammation and oxidative stress [9–11].

Moreover, current lifestyle habits mean that people spend up to 16 h in the postprandial state, which can negatively affect their metabolism. In the human body, the postprandial state is characterized by changes in macro- and micronutrient concentrations, factors produced by the gut microbiota, and endocrine signals, among others, so it is a dynamic, complex state affecting almost all our organs and tissues. The postprandial response subsequently influences the metabolism and general health status [12,13].

A previous study by the research team showed that the intake of a dietary pattern based on fruits, avocado, whole grains, and trout typical of the Colombian coffee region improved lipemia and postprandial insulinemia in obese people, suggesting that this dietary pattern could be an alternative to other heart-healthy patterns such as the Mediterranean and Nordic diets in regions where basic foods from these two diets are scarce or unavailable [14]. However, there are currently no studies assessing the effect of following this dietary model on the regulation of genes involved in obesity-associated processes such as inflammation and oxidative stress.

Our aim was to evaluate the effect of 8 weeks of consumption of foods such as fruit, avocado, whole grains, and trout on postprandial inflammatory gene expression (*NFKB1, RELA, IKKA, MMP9, TNF, IL1β, IL6*) and oxidative stress (*NFE2L2*) in obese Colombians as alternative foods to those included in other healthy models such as the Mediterranean and Nordic diets.

1. Materials and Methods

1.1. Study Design and Participants

The participants in the present study and its design were previously published [14]. In brief, the present study was a randomized controlled crossover study and the inclusion and exclusion criteria were previously published [14]. The sample size was calculated taking into account the main objective of the intervention, which was to analyze the postprandial change in triglycerides. Based on previous studies, 35 subjects were included with the aim of detecting a 15% change in postprandial triglycerides between the two dietary interventions, with a significance level of 0.05, a power of 80%, and a dropout rate of 10% [15]. After recruitment, 44 obese subjects with no diagnosed chronic diseases followed and completed the two dietary models for 8 weeks each, including 2 weeks of a washout

period between diets (Figure 1). One of the diets was composed mainly of predominant foods of the Colombian coffee-growing zone (fruits, avocado, whole grain, and trout) (FAWGT diet) and the other diet consisted of foods that the participants consumed in their normal daily life, called the usual diet (UD). The subjects were instructed not to change their daily physical activity. All study participants provided their written informed consent, and ethics committees of the Universidad de Caldas and Clinica Comfamiliar approved the study protocol; additionally, this study is registered in ClinicalTrials.gov (NTC04920409).

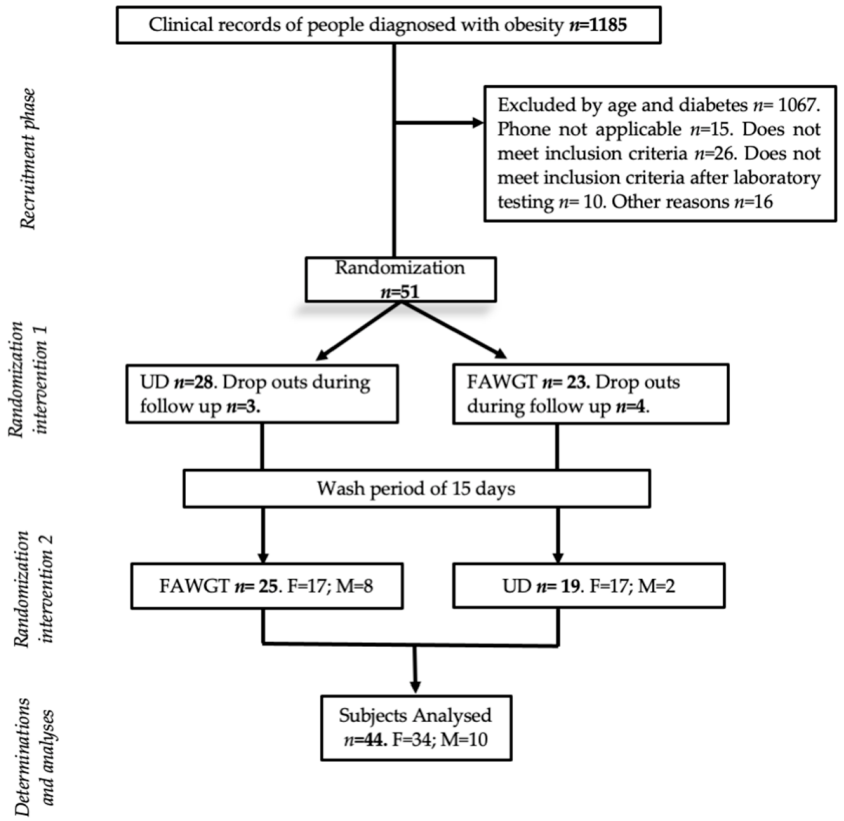

Figure 1. Flow chart of participants and study design. From 1185 medical records of patients diagnosed with obesity, 51 subjects were recruited, of whom 28 were randomized to follow the usual diet and 23 to the FAWGT diet. After 8 weeks of intervention, 7 subjects dropped out of the study and the remaining subjects changed their dietary pattern. Finally, 44 subjects completed the study. F, female; M, males; UD, usual diet; FAWGT, diet composed of fruit, avocado, whole grains, and trout.

1.2. Diet, Dietary Assessment, and Follow-Up Visits

The composition of the diets has been described in detail elsewhere [14,16]. The main differences between the diets at the nutrient level were the amount of dietary fiber and the quality of dietary fat, carbohydrates, and proteins. Both the FAWGT diet and the UD were isocaloric based on the evaluation of the habitual diet calculated from a 3-day food record before the beginning of the study. In the FAWGT diet, the main emphasis was on food items such as whole grains (*arepa* and rice), local fruits (e.g., *sweet granadilla/granadilla (Passiflora ligularis)*, *peach palm fruit/chontaduro (Bactris gasipaes)*, *cape gooseberry/uchuvas (Physalis peruviana)*, *star fruit/carambolo* (*Averrhoa carambola*), and *mango* (*Mangifera indica* L.)) and vegetables, rapeseed oil, avocado, and three fish (trout) meals per week. In the usual diet, participants were instructed to eat the foods consumed in their usual diet as part of their normal lifestyle. The usual diet was characterized by the consumption of refined cereals; foods rich in carbohydrates from bread, potato, plantain, and cassava; foods rich in saturated fat, with >50% fat especially in butter; <200 g/day of fruit and vegetables; <1 portion of any fish per week; consumption on demand of any type of meat per week;

reduced consumption of legumes (<2 times per week); and an unrestricted consumption of sugary and carbonated beverages. The recommended foods for both diets are summarized in Table S1, where the macronutrient content was based on the Recommended Energy and Nutrient Intakes (RENIs) for the Colombian population [17]. The washout period consisted of a return to the patients' usual diet characterized by a low consumption of fruit and vegetables, no fish, and whole grains.

The participants' dietary follow-up protocol consisted of three 24 h reminders (two nonconsecutive during the week and one at the weekend). The recordings were carried out at the beginning of the dietary intervention (week 0), in the middle (week 4), and at the end (week 8) [14,16,18].

1.3. Postprandial Study

The present work lies within the framework of the postintervention phase of the study (Figure S1) after 8 weeks of dietary intervention during the postprandial state. Analyses were carried out between hour 0 and hour 4 of the postprandial state to assess the postprandial response after 8 weeks of intervention. The participants consumed breakfast based on the same composition of the diet into which they had been randomized for the dietary intervention period. The composition of the breakfasts for the postprandial study is shown in Table S2. During the postprandial period, participants could only drink water. The composition of the breakfasts was previously published [14], and in the FAWGT diet, it was based on the consumption of *arepa* prepared with whole grains, oats, typical fruits of the Colombian coffee region, and yogurt. The breakfast of the usual diet was based on the consumption of eggs, butter, whole milk, *arepa* prepared with refined flour, coffee with sugar, and the traditional *buñuelo* (fried food made of flour and cheese).

1.4. Biochemical Measurements of Metabolic Parameters

EDTA blood samples were collected from the participating patients after 12 h of fasting. In the present study, samples were used after 8 weeks of dietary intervention at time 0 and 4 h of the postprandial state (Figure S1). Clinical parameters associated with lipid metabolism, glucose homeostasis, and inflammation, which have been previously published, were measured from the samples obtained.

1.5. Peripheral Blood Mononuclear Cells (PBMC) Isolation

Venous blood samples were collected after 8 weeks of dietary intervention in tubes containing 1 g EDTA/L after 12 h of fasting at 0 h and 4 h after ingestion of the breakfast. The isolation of mononuclear cells was carried out with the Ficoll gradient and the cells obtained were stored at −80 °C in RNAlater (Invitrogen RNAlater™ Stabilization Solution, Invitrogen, Waltham, MA, USA) until use [19].

1.6. Total RNA Isolation and cDNA Generation

The RNA was isolated from PBMCs using the kit Direct-zol RNA Miniprep Plus according to the manufacturer's instructions (Zymo Research, Irvin, CA, USA). The samples obtained were treated with DNAase I (AMPD-1 Kit, Sigma Aldrich, St. Louis, MO, USA), and then cDNA was obtained using the High-Capacity cDNA Synthesis Kit (Applied Biosystems, Carlsbad, CA, USA) for gene expression studies.

1.7. qRT-PCR Analysis of Gene Expression

A gene expression analysis was carried out via real-time PCR using the OpenArray platform according to the manufacturer's instructions (Thermofisher Scientific, Waltham, MA, USA). The primers used for the genes studied were obtained from the Thermofisher Scientific website (https://www.thermofisher.com/es/es/home/life-science/pcr/real-time-pcr/real-time-pcr-assays/taqman-gene-expression.html. Accessed on 20 March 2021). The genes involved in the inflammatory and oxidative stress pathways were included in the OpenArray panel: *NFKB1, RELA, IKKA, MMP9, TNF, IL1β, IL6,* and *NFE2L2*. The gene

expression was calculated with *HPR1*, *B2M*, and *GAPDH* as housekeeping genes, according to the Bestkeeper algorithm [20], and expressed as a relative expression using the equation:

$$\text{relative expression} = 2 - (\text{Ct target gene} - \text{Ct bestkeeper}).$$

The data set was analyzed using OpenArray® Real-Time qPCR Analysis Software (Applied Biosystems, Carlsbad, CA, USA).

1.8. Statistical Analysis

Statistical analyses were carried out using SPSS 20 software. The values represent the mean and standard error. A comparison between the baseline characteristics was carried out using a one-way ANOVA. A comparison of the effects between the 0 h and 4 h postprandial status after 8 weeks of dietary intervention was performed using a repeated measures analysis. In the latter, we evaluated the overall effect of the dietary intervention (global ANOVA and *p* for diet), the effect of time postprandially (*p* for time), and the diet–time interaction (diet vs. time). For multiple comparisons, we used Sidak's test. *p*-values < 0.05 were considered statistically significant. Finally, a correlation analysis was performed between the expression of inflammatory genes and the clinical and biochemical parameters of the participants using a Pearson bivariate correlation analysis with SPSS 20 for Windows software (SPSS Inc., Chicago, IL, USA), for which $p < 0.05$ was considered significant. The analysis was performed with the expression values of inflammatory genes and the values of clinical and biochemical parameters taken independently at times 0 and 4 h of the postprandial state after 8 weeks of dietary intervention for both diets—the FAWGT and usual diet.

2. Results

2.1. Effect of the Dietary Intervention on Clinical Variables of the Subjects Included in The Study

The baseline characteristics of the participants were previously published [14] (Table S3). Regarding the dietary intervention, we observed a lower weight and BMI (both $p < 0.001$) after the consumption of the FAWGT diet compared with the UD (Table 1). In contrast, no significant postprandial differences were observed after the two intervention periods in the other clinical parameters analyzed (Table S4).

Table 1. Characteristics of subjects included in the study in fasting, after and before the dietary intervention.

	FAWGT		**UD**				
Parameter	Baseline	8 weeks	Baseline	8 weeks	*p* time	*p* diet	*p* Diet vs. Time
Weight (kg_2)	88.5 ± 2.0	87.0 ± 2.0 [(a)]	88.3 ± 2.1	88.4 ± 2.1 [(b)]	<0.001	0.007	<0.001
BMI (kg/m^2)	35.7 0.6	35.1 ± 0.7	35.5 0.6	35.6 ± 0.7	0.001	0.015	<0.001
Fat (%)	42.7 ± 0.5	41.9 ± 0.6	42.4 ± 0.7	42.1 ± 0.6	0.006	0.748	0.285
Waist–hip ratio	0.90 ± 0.02	0.90 ± 0.01	0.91 ± 0.01	0.92 ± 0.01	0.488	0.017	0.764
Systolic blood (mmHg)	122.1 ± 1.8	119.8 ± 1.6	120.15 ± 1.9	120.0 ± 1.9	0.267	0.539	0.364
Diastolic blood (mmHg)	78.6 ± 1.4	77.6 ± 1.2	80.1 ± 1.2	77.6 ± 1.3	0.850	0.450	0.313
Glucose (mg/dL)	94.3 ± 1.6	94.4 ± 2.0	95.9 ± 1.7	96.0 ± 2.0	0.923	0.079	0.935
Insulin (mUI/mL)	22.5 ± 1.9	21.6 ± 1.4	20.16 ± 1.2	24.3 ± 1.8 [(a,b)]	0.870	0.399	0.016
Total Cholesterol (mg/dL)	201.3 ± 5.5	201.3 ± 5.6	202.0 ± 5.3	200.4 ± 5.4	0.764	0.962	0.765
HDL-c (mg/dL)	40.1 ± 1.5	41.0 ± 1.4	43.4 ± 1.6 [(b)]	41.6 ± 1.6 [(a)]	0.494	0.005	0.039
Non-c HDL-c (mg/dL)	161.1 ± 5.8	160.3 ± 5.5	159.3 ± 5.5	159.0 ± 5.6	0.840	0.525	0.936
LDL-c (mg/dL)	118.4 ± 5.4	124.3 ± 5.3	118.0 ± 5.3	118.8 ± 4.8	0.212	0.303	0.439
TG (mg/dL)	198.2 ± 13.4	182.7 ± 10.1	191.2 ± 13	200.9 ± 14.3	0.726	0.444	0.100
CRP (mg/L)	4.35 ± 0.4	5.0 ± 0.5	4.6 ± 0.4	5.2 ± 0.4	0.002	0.326	0.898

FAWGT, diet rich in fruit, avocado, whole grains, and trout. UD, usual diet. Values represent the mean± standard error. The analyses correspond to ANOVA for repeated measures, where *p* time is the kinetics of the dietary intervention response; *p* diet is the influence of diet; and *p* Diet vs. Time is the interaction of the two factors. When post hoc tests were pertinent, we used multiple comparisons with Sidak correction. (a) $p < 0.05$ by comparison to baseline values in the diet. (b) $p < 0.05$ between diets at the same time.

2.2. Effect of the Dietary Intervention on the Postprandial Expression of the Inflammatory-Related Genes

The intake of the FAWGT diet for 8 weeks decreased the postprandial expression (4 h after meal intake) of the *NFKB1* gene compared to the fasting state ($p < 0.001$). In addition, the postprandial expression of the *NFKB1* gene was lower after the FAWGT diet than after the UD diet ($p < 0.001$) (Figure 2A).

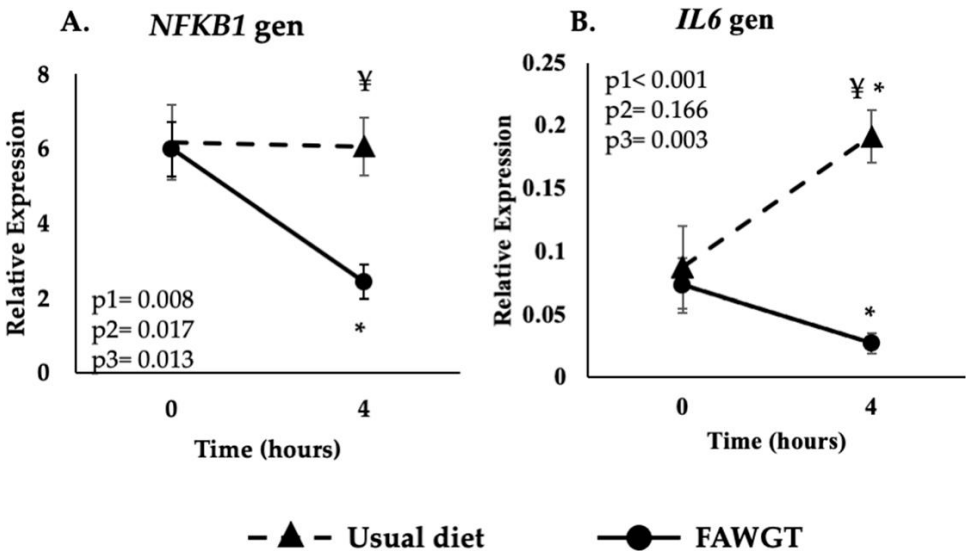

Figure 2. Postprandial expression of the inflammatory-related *NFKB1* (**A**) and *IL6* (**B**) genes after 8 weeks of dietary intervention with a usual diet and the diet consisting of fruit, avocado, whole grains, and trout predominant in the Colombia coffee region (FAWGT). Values are shown as mean ± S.E.M of the relative expression. The analyses correspond to ANOVA for repeated measures where p1: diet influence; p2: time, the kinetics of the postprandial response; and p3: diet–time interaction (diet vs. time). For multiple comparisons, we used the Sidak test. * $p < 0.05$ 4 h vs. fasting state, ¥ $p < 0.05$ between diets at the same time.

Moreover, the intake of the FAWGT diet for 8 weeks decreased the postprandial expression of the *IL6* gene compared to the fasting state ($p = 0.013$) (Figure 2B). In contrast, the intake of the UD diet for 8 weeks increased the postprandial expression of the *IL6* gene compared to the fasting state ($p = 0.027$). In addition, the postprandial expression of the *IL6* gene was lower after the FAWGT diet than after the UD diet ($p < 0.001$) (Figure 2B).

The consumption of the FAGWT diet decreased the *IL1β* postprandial gene expression compared to the fasting state ($p < 0.001$). The *IL1β* gene expression was higher after the UD diet at both the fasting ($p = 0.039$) and postprandial state ($p < 0.001$) than after the consumption of the FAGWT diet (Figure 3A). In the other genes, no significant differences were found between the two diets.

2.3. Effect of the Dietary Intervention on the Postprandial Expression of the Oxidative Stress Gen

Finally, *NFE2L2* postprandial gene expression was higher after the consumption of the UD than after the FAWGT diet ($p = 0.008$) (Figure 3B).

2.4. Correlation Analysis between the Gene Expression of the Inflammatory and Oxidative Stress-Related Genes and Biochemical Parameters

We observed a relationship between *NFKB1* gene expression and triglyceride levels 4 h after meal intake ($r^2 = 0.3241$ and $p = 0.032$) after the consumption of the FAGWT diet (Figure 4). Moreover, the relative expression of *IL1β* was directly related to insulin levels at 4 h after the meal ($r^2 = 0.3168$ and $p = 0.0361$) with the UD (Figure 5).

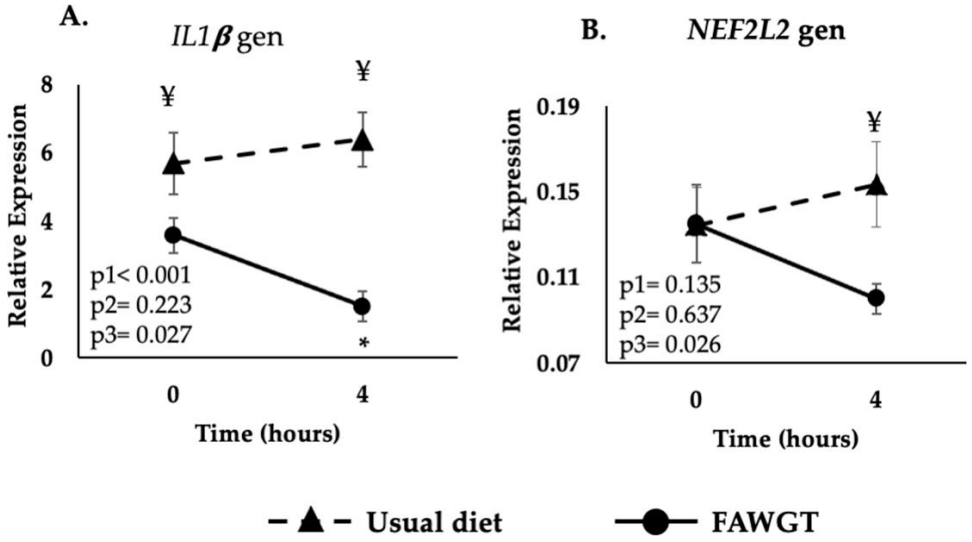

Figure 3. Postprandial expression of the inflammatory-related *IL1β* (**A**) and oxidative-stress-related *NFE2L2* (**B**) gene after 8 weeks of dietary intervention with a usual diet and the diet consisting of fruit, avocado, whole grains, and trout predominant in the Colombia coffee region (FAWGT). Values are shown as mean ± S.E.M of the relative expression. The analyses correspond to ANOVA for repeated measures where p1: diet influence; p2: time, the kinetics of the postprandial response and p3: diet–time interaction (diet vs. time). For multiple comparisons, we used the Sidak test. * $p < 0.05$ 4 h vs. fasting state, ¥ $p < 0.05$ between diets at the same time.

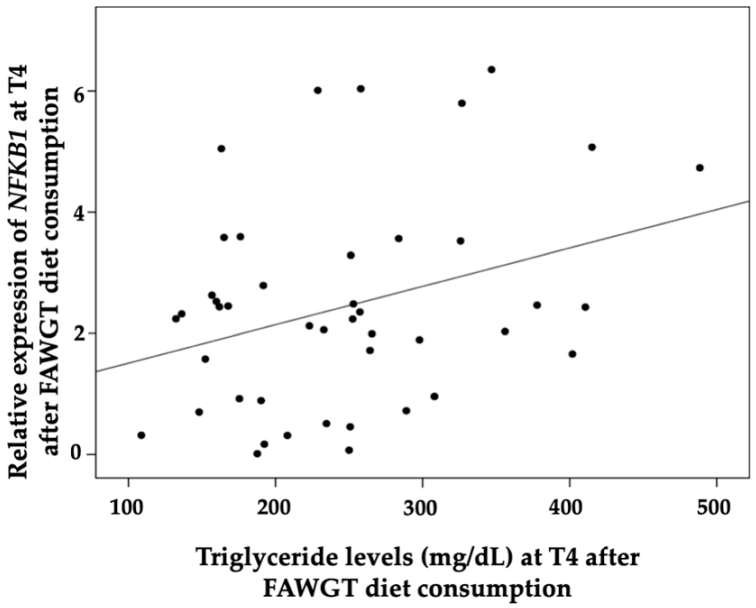

Figure 4. Correlation analysis between the gene expression of the inflammatory-related *NFKB1* and triglyceride levels in the postprandial state at 4 h after 8 weeks of dietary intervention with a diet consisting of fruit, avocado, whole grains, and trout predominant in the Colombia coffee region (FAWGT). The correlation was evaluated with a Pearson bivariate correlation analysis using SPSS 20 for Windows software (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered to be significant.

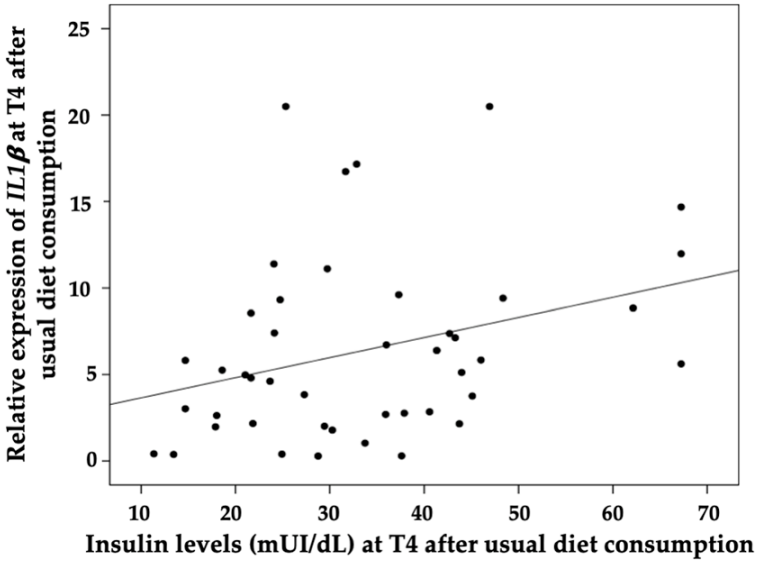

Figure 5. Correlation analysis between the gene expression of the inflammatory-related *IL1β* and the insulin levels in the postprandial state at 4 h after 8 weeks of intake of a usual diet. Correlation was evaluated with a Pearson bivariate correlation analysis using SPSS 20 for Windows software (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered to be significant.

Discussion

Overweight and obesity currently constitute a major global public health problem, which is closely linked to the development of type 2 diabetes mellitus and cardiovascular disease. Previous studies have demonstrated the beneficial effect of healthy diets (Mediterranean and Nordic) on the regulation of genes associated with the development of these diseases. However, it is not possible to adhere to these dietary patterns in all regions of the world due to the cost and availability of foods. We aimed to evaluate the effect of the 8-week consumption of foods such as fruit, avocado, whole grains, and trout on postprandial inflammatory and oxidative stress gene expression in obese Colombians as alternative foods to those included in other healthy dietary models.

In a previous study, we described, in the same population that we had previously found, in the postprandial state, an increase in postprandial triglycerides, VLDL-c, and insulin levels after ingestion of the two diets; however, this increase was greater in the usual diet than in the diet based on fruit, avocado, whole grains, and trout (FAWGT diet) [14].

Here, our results show that in obese people, the intake for 8 weeks of the FAWGT diet decreases the postprandial expression of inflammatory (*NFKB1*, *IL6*, *IL1β*) and oxidative stress (*NFE2L2*) genes when compared with the intake of the usual diet. Finally, the postprandial expression of the *NFkB1* and *IL1β* genes correlated positively with triglyceride and insulin levels after the dietary intervention with the FAWGT diet and UD, respectively. Obesity is the result of a complex interaction between genetic, metabolic, and environmental factors including dietary habits [21]. It has now reached pandemic proportions with an increase from 108 million people in 1982 to 422 million in 2014 [22]. If this trend continues, by 2030, more than 57.8% (3.3 billion people) of the world's adult population will be overweight or obese [23]. Obesity has been associated with chronic low-grade inflammation and oxidative stress [24] characterized by the production of adipokines, proinflammatory cytokines, and reactive oxygen species, which are involved in the development of chronic noncommunicable diseases [1,25]. Moreover, the lifestyle of current society leads people to spend most of the day in a postprandial state. Staying in this state for more than 16 h leads to low-grade chronic inflammation, which is associated with the development of diseases [26].

Our nutrigenomic approach is based on the fact that nutrients and bioactive dietary compounds can modify gene expression. The discovery of these gene–nutrient interactions

will help the use of customized diets. In line with this, this knowledge may allow for the design of dietary strategies focused on the reduction in the expression of inflammatory or oxidative stress genes, which is especially important in the case of noncommunicable diseases such as obesity, which are currently considered an important world public health problem [27].

In fact, previous studies have shown the effect of diet or its components on the molecular mechanisms associated with inflammatory activity and oxidative stress [28]. One study showed that the use of a Mediterranean diet model induced the downregulation of proinflammatory and endoplasmic reticulum stress genes, even after coenzyme Q10 supplementation, versus a diet model rich in saturated fats [29]. Additionally, the Nordic diet showed that this model reduced subcutaneous adipose tissue and inflammatory genes such as *IRF1*, *CD67*, *IL-32*, and *IL6R* compared to a control diet [30].

In the present study, the decrease in the postprandial expression of the proinflammatory genes (*NFKB1*, *IL6*, and *IL1β*) could have been due to the fact that the *NFKB1* gene encodes for the p50 protein, a subunit of the transcription factor NF-kB, which activates the transcription of proinflammatory genes (*TNF-α*, *IL1β*, *IL6*, among others), which regulate the inflammatory response [31]. The decreased postprandial expression of *IL6* and *IL1β* after 8 weeks of dietary intervention could be associated with the lower activation of the NF-kB transcription factor signaling pathway induced by the intake of healthy fatty acids from trout and avocado (omega 3, MUFA, and PUFA), which also improves postprandial triglyceride levels and glucose homeostasis [14,32,33].

In this context, a previous study showed that the consumption of a healthy Nordic dietary model induced the postprandial downregulation of inflammatory genes such as *TLR4, IL18*, and *CD36* and upregulated the expression of *PPARD* compared to a control diet in a population with metabolic syndrome [10], demonstrating, as in our study, that the consumption of healthy dietary patterns beneficially impacts the gene expression profile.

In line with the above, our observations may be explained by the composition of the FAWGT diet, characterized by the consumption of trout containing 1.4 g omega-3 (280 mg EPA and 160 mg DHA per 100 g) in addition to other nutrients such as selenium and vitamin D, among others [34]. Avocado also contains monounsaturated fatty acids, fiber, and phytonutrients, and both omega-3 and monounsaturated acids have been shown to regulate inflammatory markers. Thus, omega-3 fatty acids may act as ligands of the peroxisome-activated receptor (PPARγ), a transcription factor that activates the expression of related genes with the inflammatory cascade [35–37]. Docosahexaenoic acid (DHA) inhibits the synergistic effect between palmitic acid and lipopolysaccharide (LPS) on the expression of proinflammatory genes via NF-kB [38]. Additionally, in vitro studies showed that avocado consumption decreased the concentration of proinflammatory molecules such as IL1β, IL6, and TNF-α through the modulation of the NF-kB factor [39]. Thus, these characteristics of the FAWGT diet account for a reduction in the inflammatory state, as suggested by the expression of the genes shown in this work.

In addition, the FAWGT diet also involves the consumption of typical fruit from the Colombian coffee region (e.g., *granadilla, chontaduro, uchuvas, carambolo,* and *mango*), which are rich in vitamins (C and D) and phenolic compounds with antioxidant power (β-carotenes and tocopherol) [40]. A previous in vitro study showed that in mononuclear cells, a multivitamin complex rich in b-carotenes, vitamin C, and tocopherol had an antioxidant and anti-inflammatory effect in patients with type 1 diabetes and decreased the production of proinflammatory cytokines IL6 and TNF-α and increased IL4 [41]. Moreover, the daily intake of 400 g/d of whole fruit (banana, tangerine, apple, strawberry, orange, peach, grape, and mango) for 14 days in young Colombians between 18 and 30 years old induced a reduction in the mRNA expression of *IL6R* and *RELA* genes and an increase in HDL cholesterol levels compared to a control group [42]. Another study demonstrated that the intake of *mango* tea had therapeutic potential in treating obesity and related dis- eases by regulating the expression of transcriptional factors and enzymes associated with adipogenesis [43].

The transcription factor NRF2 (encoded by the *NFE2L2* gene) regulates genes related to oxidative stress, which is directly associated with the inflammatory response [44]. In line with this, the current work showed a postprandial reduction in *NFE2L2* gene expression by the FAWGT diet, while the consumption of the UD had the opposite effect. These findings suggest that the effect of diet on the downregulation of inflammation, and therefore oxidative-stress-related genes, is due to a synergy between the main foods that constitute the dietary model, including the healthy fatty acids of animal and vegetable origin and local fruit, among others.

One limitation of this work is that the aim was to examine the effects of the FAWGT diet on the expression of some proinflammatory genes in peripheral blood mononuclear cells; however, the protein levels were not determined, which prevented us from relating gene expression with protein levels. Another limitation may be the small sample size; however, the study design allowed us to detect the net effect of the intervention with small working groups. The duration of the intervention period might be a limitation, and additional diet effects could be detected in a longer intervention. This should be taken into account for the extrapolation of the results, suggesting that further studies are needed to confirm our findings. On the other hand, one of the strong points of our study was the design; a randomized crossover study reduces interindividual variation, which allowed us to obtain reliable scientific evidence.

3. Conclusions

In conclusion, our results suggest that the consumption of a diet based on fruit, avocado, whole grains, and trout for 8 weeks reduces the postprandial inflammatory state, and can therefore be considered a valid alternative to other heart-healthy diets, since it improves the molecular regulation of the genes involved in the immune response and oxidative stress in obese subjects and demonstrates a beneficial effect at the postprandial state similar to other healthy diets.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/nu15020306/s1: Figure S1: Study design; Table S1: Recommended foods in the study; Table S2: Composition and caloric distribution of the breakfasts used in the postprandial study; Table S3: Baseline characteristics of the patients included in the study before any dietary intervention; Table S4: Postprandial changes in the biochemical parameters after 8 weeks of dietary intervention.

Author Contributions: Conceptualization, D.M.M.-P. and C.H.G.-C.; formal analysis, D.M.M.-P. and O.A.R.-Z.; funding acquisition, D.M.M.-P.; investigation, D.M.M.-P., E.Y.A.M. and J.C.C.-H.; methodology, E.Y.A.M., M.S.-G. and J.C.C.-H.; resources, J.L.-M., A.C. and O.A.R.-Z.; supervision, C.H.G.-C., A.C. and O.A.R.-Z.; validation, E.Y.A.M.; writing—original draft, D.M.M.-P.; writing—review and editing, D.M.M.-P., A.C., O.A.R.-Z. and C.H.G.-C. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by the Colombian Ministry of Science and Innovation (COLCIENCIAS) with a grant awarded under the National PhD Call 647 of 2014. This study was funded by the University of Caldas in the "General call for the financing of Research, Innovation and Creation of the University of Caldas 2015 (0406716)" and the "General call for project financing of Research, research-creation and innovation 2016 (0179217)" to D.M.M.-P. and C.H.G.-C. Convocatoria 7 Universidad Libre Seccional Pereira 2017 (14010104) to D.M.M.-P. This study was also partially supported by the Instituto de Salud Carlos III under the grants CP14/00114, PI19/00299, DTS19/00007, and PI22/00925 to A.C.; CP19/00142 and PI22/01020 to O.A. R.-Z.. O.A.R.-Z. and A.C. are supported by an ISCIII research contract (Programa Miguel-Servet CP19/00142 and CPII19/00007, respectively).

Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of University Of Caldas And Clinical Comfamiliar Risaralda, Colombia (protocol code 0406716 approved by act 10 of 2015 from University of Caldas).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author C.H.G.-C. and the principal researchers of the project D.M.M.-P. and C.H.G.-C.

Acknowledgments: We would like to thank the PhD professors in Biomedical Sciences of the Colombian coffee region for their contributions. Our thanks also go to Andrés Morales for his technical contributions in conducting the tests at the Maimonides Institute of Biomedical Research of Cordoba, Spain (IMIBIC); to Industrias Alimenticias Monserrat for supplying the dark chocolate for the participants; and special thanks to IMIBIC for making its entire infrastructure available to us.

Conflicts of Interest: The authors declare no conflict of interest.

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CAPITULO V: Efecto de una dieta rica en frutas, verduras, aguacate, granos enteros y trucha sobre la microbiota intestinal de mujeres con obesidad.

Capitulo V: Efecto de una dieta rica en frutas, verduras, aguacate, granos enteros y trucha sobre la microbiota intestinal de mujeres con obesidad

Artículo en preparación

Efecto de una dieta rica en frutas, verduras, aguacate, granos enteros y trucha sobre la microbiota intestinal de mujeres con obesidad.

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Key words: Obesity, Diet, gut microbiota, inflammation, dysbiosis

Resumen

La obesidad es un factor causal de enfermedades crónicas no transmisibles, las cuales son la primera causa de mortalidad en el mundo. El vínculo entre estas dos condiciones es una inflamación crónica de bajo grado y una de las causas de esta inflamación, podría ser un desbalance en la composición de la microbiota intestinal**.** Se realizó un estudio randomizado, paralelo, controlado, con 29 mujeres colombianas, con un índice de masa corporal >30 Kg/m^2, quienes fueron sometidas a una de dos dietas; la dieta FAWGT que se caracterizó por un mayor consumo de frutas y verduras, aguacate, granos enteros (maíz y arroz) y trucha, o la dieta usual (UD) caracterizada por un alto consumo de grasas saturadas y carbohidratos procesados. Después de 8 semanas de intervención se realizó un análisis de la composición de la microbiota intestinal usando la plataforma 454 Life Sciences (Roche) Junior plataform, de acuerdo a los protocolos estándar de la plataforma 454. Se encontró una disminución en la abundancia relativa de la familia Vellionellaceae con la dieta FAWGT y una disminución de la abundancia relativa del género Roseburia con la UD. Aunque se requieren estudios con mayor duración, la dieta FAWGT podría ser una alternativa a otras dietas saludables.

Abstract

Obesity is a causal factor of chronic non-communicable diseases, which are the leading cause of mortality in the world. The link between these two conditions is a chronic low-grade inflammation and one of the causes of this inflammation could be an imbalance in the composition of the intestinal microbiota. A randomized, parallel, controlled study was conducted with 29 Colombian women, with a body mass index >30 kg/m2, who were subjected to one of two diets; the FAWGT diet which was characterized by a higher consumption of fruits and vegetables, avocado, whole grains (corn and rice) and trout, or the usual diet (UD) characterized by a high consumption of saturated fats and processed carbohydrates. After 8 weeks of intervention, an analysis of gut microbiota composition was performed using the 454 Life Sciences (Roche) Junior platform, according to standard 454 platform protocols. We found a decrease in the relative abundance of the family Veillionellaceae with the FAWGT diet and a decrease in the relative abundance of the genus Roseburia with the UD. Although longer duration studies are required, the FAWGT diet could be an alternative to other healthy diets.

Introducción

Las enfermedades crónicas no transmisibles (ECNT), que incluyen enfermedad cardiovascular, diabetes Mellitus tipo 2 y algunos tipos de cáncer entre otras, ocasionan el 70% de las muertes prematuras en el mundo. La obesidad es el principal factor de riesgo para el desarrollo de estas enfermedades y está asociada a una disminución en la expectativa de vida de las personas que la padecen (1). La prevalencia de la obesidad ha aumentado en dimensiones pandémicas en los últimos 50 años. Los cambios en el sistema alimentario mundial junto con el aumento del comportamiento sedentario parecen ser los principales impulsores de esta pandemia. El vínculo entre la dieta, los nutrientes y el sistema inmunológico está dado por una compleja red de señales, sin embargo, se hace necesario incluir factores como la composición de la microbiota intestinal (MI), antecedentes genéticos y estilo de vida (2).

La MI es una comunidad simbiótica, que actúa como un órgano que está integrado con el metabolismo del huésped . La MI influye en aspectos como: la extracción de energía de los alimentos, el metabolismo de lípidos, la respuesta inmune, las funciones endocrinas, el contenido de lipopolisacárido, la producción de ácidos grasos de cadena corta (AGCC), la vía de señalización de la insulina entre otros procesos (3) . Puede ser modulada por factores como: el sexo, la edad, la ubicación geográfica, el uso de antibióticos y la dieta (4). Reese and Dunn, sugieren que la diversidad en la comunidad microbiana podría estar asociada de manera positiva con la diversidad en la dieta (5).

Algunos estudios previos, evidencian el efecto de dietas mixtas o de algún nutriente específico sobre la microbiota intestinal (6). Uno de ellos, evidenció una disminución de la relación Firmicutes/Bacteriodota, en 51 participantes con hiperlipidemia, suplementados durante 12 semanas, con ácidos grasos poliinsaturados tipo ω 3 de origen vegetal, lo que podría tener beneficios en el metabolismo de lípidos y en la salud intestinal (7). En una población similar, Moreno-Indias et al, reportaron un incremento en la abundancia relativa de géneros como: Bifidobacterium y Lactobacillus, protectores de la integridad intestinal, y de los géneros

Faecalibacterium prausnitzii y Roseburia, productores de butirato, además, una disminución en la abundancia de bacterias productoras de lipopolisacárido (LPS) como: Escherichia coli y Enterobacter cloacae ,en personas con hiperlipidemia, después de un consumo moderado de vino tinto durante 4 semanas, posiblemente por el contenido de polifenoles en el vino (8). Otro estudio, mostró como una dieta con bajo consumo de vegetales, se relacionó con un mayor recuento de leucocitos, parte de este efecto estuvo mediado por el género Collinsella, que se ha relacionado con el consumo de comidas procesadas y con hígado graso (9).

El microbioma intestinal humano es un ecosistema complejo, formado no solo por bacterias, sino también hongos, arqueas, bacteriófagos y protozoos. Es así como, en una revisión sistemática que incluyo 17 ensayos clínicos, evaluaron el efecto de la dieta mediterránea sobre la abundancia y la diversidad de la microbiota intestinal, no encontrando evidencia suficiente para establecer esta relación (10). Sin embargo, estudios aislados muestran un efecto benéfico de este patrón dietario sobre la microbiota intestinal y su relación con parámetros metabólicos e inflamatorios. Vítale y colaboradores, reportaron un incremento en la abundancia de Intestinimonas butyriciproducens y Akkermansia muciniphila y una mayor producción de butirato en estado postprandial lo que se relacionó con un aumento en la sensibilidad a la insulina con el consumo de una dieta mediterránea, durante 8 semanas, en comparación con un patrón de dieta occidental (11).

En las sociedades modernas occidentales, los hábitos alimentarios se caracterizan por una disminución en el consumo de fibra alto contenido de proteínas de origen animal, grasas saturadas, cereales refinados, azúcar, alcohol, sal y fructosa derivada del jarabe de maíz, con un consumo reducido consumo de frutas y verduras (12). Este tipo de dieta contribuye directamente al desarrollo de obesidad, síndrome metabólico y enfermedades cardiovasculares (13).

El objetivo de este estudio fué determinar si una dieta suplementada con frutas, verduras, granos enteros (arepa y arroz) aguacate y trucha, disponibles en la región cafetera colombiana, modifica la microbiota intestinal de mujeres con obesidad.

Materiales y Métodos

Población

El presente estudio incluyó 29 mujeres con obesidad entre 45 y 60 años de edad, con un IMC > a 30 kg/m2, sin diagnóstico de enfermedad cardiovascular, falla hepática, renal o tiroides, pero se incluyeron mujeres con dislipidemia. Igualmente fueron incluidas no fumadoras, no consumidoras regulares de alcohol y aquellas que no estuvieran participando en programas de reducción de peso.

El reclutamiento de las participantes fue realizado entre octubre de 2017 y junio de 2018. La muestra fue una subpoblación de un estudio previo realizado por el grupo de investigación. Se evaluaron 1185 historias clínicas de personas diagnosticadas con obesidad. 51 personas fueron incluidas en el estudio, 7 de las cuales tenían hipertensión y 23 algún tipo de dislipidemia. 29 mujeres recogieron la muestra de materia fecal. El estudio fue llevado a cabo en la "Clínica Comfamiliar" en Pereira, Colombia. Todas las participantes firmaron un consentimiento informado antes de empezar el estudio y fueron aconsejadas para continuar con su actividad física y su estilo de vida usual. El protocolo de este estudio fue aprobado por el comité de ética de la Universidad de Caldas (Código del proyecto No: 0406716) y el comité de ética de la Clínica Comfamiliar, de acuerdo con la declaración de Helsinki y registrado en ClinicalTrials.gov (NTC04920409).

Diseño del estudio

Se realizó un estudio paralelo controlado aleatorizado. Las voluntarias siguieron uno de dos modelos dietéticos durante 8 semanas. La aleatorización se realizó siguiendo una lista de asignación informatizada utilizando el software Excel (Microsoft Office 2015, Excel 2013) (Figura 1). Las dietas durante el periodo de intervención fueron: (1) una dieta suplementada con frutas, verduras, aguacate, granos integrales y trucha (FAWGT diet,), por sus siglas en inglés; y (2) la dieta usual consumida por las participantes (UD), por sus siglas en ingles.

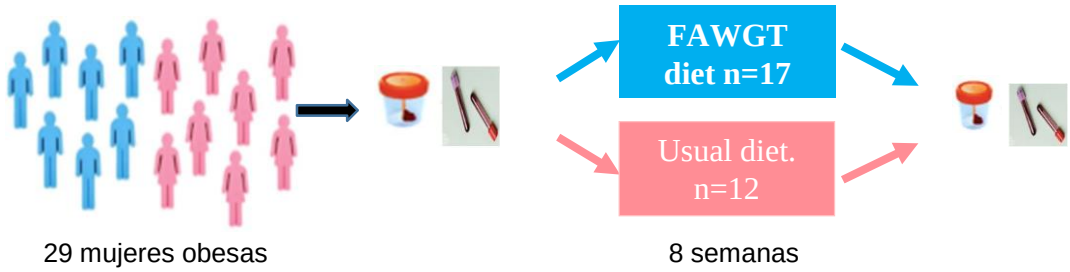

Figura 1. Diagrama del diseño del estudio

Composición de las dietas.

La composición de las dietas fue descrita en un estudio previo (14). En síntesis, la UD consistió en 16% de proteína, 54% de carbohidratos y 30% de grasa de la cual el 15% fueron grasas saturadas, 10% monoinsaturadas y 5% poliinsaturadas, del contenido calórico total. La dieta FAWGT estuvo constituida por 15% de proteína, 55% de carbohidratos y 30% de grasa de la cual menos del 10% fueron ácidos grasos saturados (AGS), 14% de ácidos grasos monoinsaturados (AGM) y 6% de ácidos grasos poliinsaturados (AGPI, del contenido calórico total. Esta dieta se basó en alimentos con propiedades antiinflamatorias y antioxidantes, disponibles en la región cafetera colombiana. Para asegurar la adherencia a la dieta, algunos alimentos fueron proporcionados a las participantes como: el pescado (trucha), granos enteros (arepa, arroz y avena), grasas (aguacate), y algunas frutas típicas de la región (granadilla, chontaduro, uchuvas, carambolo entre otras), La principal diferencia entre las intervenciones fue la cantidad de fibra y la calidad de las grasas, carbohidratos y proteínas.

La determinación de la composición de ambas dietas se hizo a través de 6 recordatorios de 24 horas: 3 al inicio y 3 al final de la intervención. Para calcular los macro y micronutrientes se utilizó el software Nutritionist Pro version 7.4.0 (Axxya Systems, Woodinville, WA, USA).

Parámetros bioquímicos y de inflamación.

Después de 12 horas de ayuno, se recolectaron muestras de sangre venosa en tubos con EDTA. Se procedió a separar el plasma por centrifugación a 1500 g por 15 minutos a 4 ºC. El plasma fue alicuotado y almacenado a -80 ºC hasta su procesamiento. La glicemia, insulinemia, CT, Colesterol HDL (cHDL), Triglicéridos (TG) y la proteína C reactiva (PCR) fueron analizados en un analizador COBAS Hitachi usando reactivos específicos (Roche, Basel, Switzerland), con métodos colorimétricos y enzimáticos. El Colesterol LDL (cLDL) fue calculado con la ecuación de Friedewald (15) y el Colesterol VLDL (cVLDL) fue calculado con la formula TG/5. La evaluación de la resistencia a la insulina se calculó con el índice (HOMA-IR) utilizando la siguiente formula:

HOMA-IR = Insulinemia en ayunas (µU/mL) * glicemia en ayunas (mg/dL) /405.

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Extracción del ADN

Se recogieron muestras de materia fecal al inicio y al finalizar la intervención, las cuales fueron almacenadas a -80 ºC. La extracción del ADN, de estas muestras, se realizó utilizando el QIAamp DNA Stool Mini Kit Handbook (QIAGEN), siguiendo las instrucciones de la casa manufacturera. El ADN se cuantifico usando un espectrofotómetro NanoDrop ND-1000v3.5.2 (NanoDrop Technology) y se almacenó a -20 ºC.

Análisis de la Microbiota

Un total de 58 muestras de materia fecal, (29 basales y 29 después de 8 semanas de la intervención dietaría) fueron usadas para el análisis de la comunidad microbiana usando el 454 Life Sciences (Roche) Junior platform, de acuerdo con los protocolos de la plataforma 454.

Análisis Filogenético

Las muestras fueron procesadas y analizadas usando Quantitative Insights into Microbial Ecology (QIIME) pipeline (versionv1.8.0;http://qiime.org/) con parámetros predeterminados.

Análisis estadístico

Todos los datos se presentan como mediana y rango interquartil (RIQ). Para el análisis estadístico se usó el software SPSS, versión 25.0 (IBM Inc.). La distribución de los datos se evaluó con el test de Kolmogórov-Smirnov. La abundancia relativa de taxones a nivel de genero se evaluó a través de un análisis LEfSe (Análisis discriminante lineal, efecto-tamaño). LEfSe determina las unidades taxonómicas operativas, que tienen más probabilidades de explicar las diferencias entre clases combinando pruebas estándar de significancia estadística (pruebas de Kruskal Wallis y Wilcoxon) junto con análisis adicionales para medir la magnitud del fenómeno observado clasificando la consistencia biológica y relevancia del tamaño del efecto (15). Se utilizaron puntuaciones LDA de 2 y un valor p para la prueba de Wilcoxon de 0,05 para identificar los géneros que se enriquecieron con respecto a los puntos temporales iniciales en cada intervención dietética o con respecto a la otra dieta en la comparación de la abundancia de géneros en el punto temporal final.

Se realizaron análisis de correlación entre los distintos parámetros utilizando el coeficiente de correlación de Spearman. Un valor $p < 0.05$ fue considerado significativo.

Resultados

Características iniciales de la población de estudio.

No se observaron diferencias significativas ($p>0,05$) en las características iniciales entre los grupos. El promedio de IMC de las participantes fue de 35,9 y 34,1 Kg/m^2 para el grupo de la dieta FAWGT y para la Dieta control respectivamente (Tabla 1).

Tabla 1. Características antropométricas y bioquímicas iniciales de las participantes.

	FAWGT Diet n= 17	**RIQ**	**UD n=12**	**RIQ**	**p value**
Índice de masa corporal ($Kg/m^{2)}$	35,90	7,90	34,05	9,22	0,549
Grasa (%)	44,70	2,90	44,00	3,85	0,535
Presión sanguínea sistólica (mmHg)	120,00	18,00	119,00	13,25	0,562
Presión sanguínea diastólica (mmHg)	80,00	11,00	80,00	9,25	0,769
Indice cintura cadera	0,90	0,16	0,88	0,15	0,436
Insulin (mUI/ml)	20,69	12,93	18,88	10,29	0,492
Glucose (mg/dl)	96,00	10,50	98,00	11,25	0,562
HOMA-IR	5,10	3,29	4,36	2,52	0,642
TC (mg/dl)	181,30	64,00	179,50	47,75	0,610
HDL-c (mg/dl)	45,00	13,50	46,00	13,00	0,876
LDL-c (mg/dl)	104,04	60,11	91,17	81,98	0,465
VLDL-c (mg/dl)	30,74	18,23	34,46	62,02	0,674
TG (mg/dl)	153,70	91,15	172,30	86,33	0,674
hs-CRP (mg/L)	5,23	4,56	6,68	2,11	0,156

Los datos se muestran como mediana y rango interquartil (RIQ). HOMA-IR: Modelo de evaluación del homeostasis de la insulina; TC: total cholesterol; HDL-c: high-density lipoproteins; LDL-c: low-density lipoproteinas; VLDL-c: very low-density lipoprotein; TG: triglycerides; hs-CRP: C-reactive protein.

Efecto de la intervención dietaría sobre las variables metabólicas.

No se observaron diferencias estadísticas ($p>0.05$) en las principales variables bioquímicas entre los grupos después de 8 semanas de intervención. Tabla 2.

Efecto de la intervención dietaría sobre macro y micronutrientes.

Después de 8 semanas de intervención en el grupo de la dieta FAWGT se observó una disminución en AGS de 9,97% a 7,25% ($p<0,001$), AGPI de ($p < 0,001$) y en la relación $\omega3/\omega6$ de 12,04 a 3,47 ($p=0,002$) y un aumento de AGMI de 10,78% a 12,44% ($p<0,001$), fibra de 13 a 34,15 g/d ($p<0,001$) vitamina C y E ($p< 0,001$) entre otros nutrientes. **Table 2.**

Tabla 2. Cambios en parámetros bioquímicos

		FAWGT Diet n=17				UD n=12				p value
	Unit	Basal		Final		Basal		Final		
Insulin	mUI/ml	20,69	12,93	16,42	14,34	18,88	10,29	18,33	7,91	0,854
Glucose	mg/dl	96,00	10,50	90,00	16,00	98,00	11,25	91,00	11,03	0,377
HOMA		5,10	3,29	3,95	3,43	4,36	2,52	3,98	2,57	0,901
CT	mg/dl	181,30	64,00	204,00	62,50	179,50	47,75	169,50	36,95	0,558
cHDL	mg/dl	45,00	13,50	40,00	12,00	46,00	13,00	38,75	14,00	0,416
cLDL	mg/dl	104,04	60,11	123,18	48,86	91,17	81,98	95,51	32,68	0,250
cVLDL	mg/dl	30,74	18,23	27,42	20,65	34,46	62,02	39,74	35,58	0,681
TG	mg/dl	153,70	91,15	137,10	103,25	172,30	86,33	198,70	177,90	0,681
PCR	mg/L	5,23	4,56	4,70	5,48	6,68	2,11	6,49	1,75	0,344

Los datos están expresados como mediana y rango interquartil. HOMA-IR; Modelo de evaluación de la homeostasis de la insulina; CT: Colesterol total; c-HDL-c: lipoproteínas de alta densidad; c- LDL: lipoproteínas de baja densidad; c-VLDL: lipoproteínas de muy baja densidad; TG: triglicéridos; PCR: proteína C reactiva.

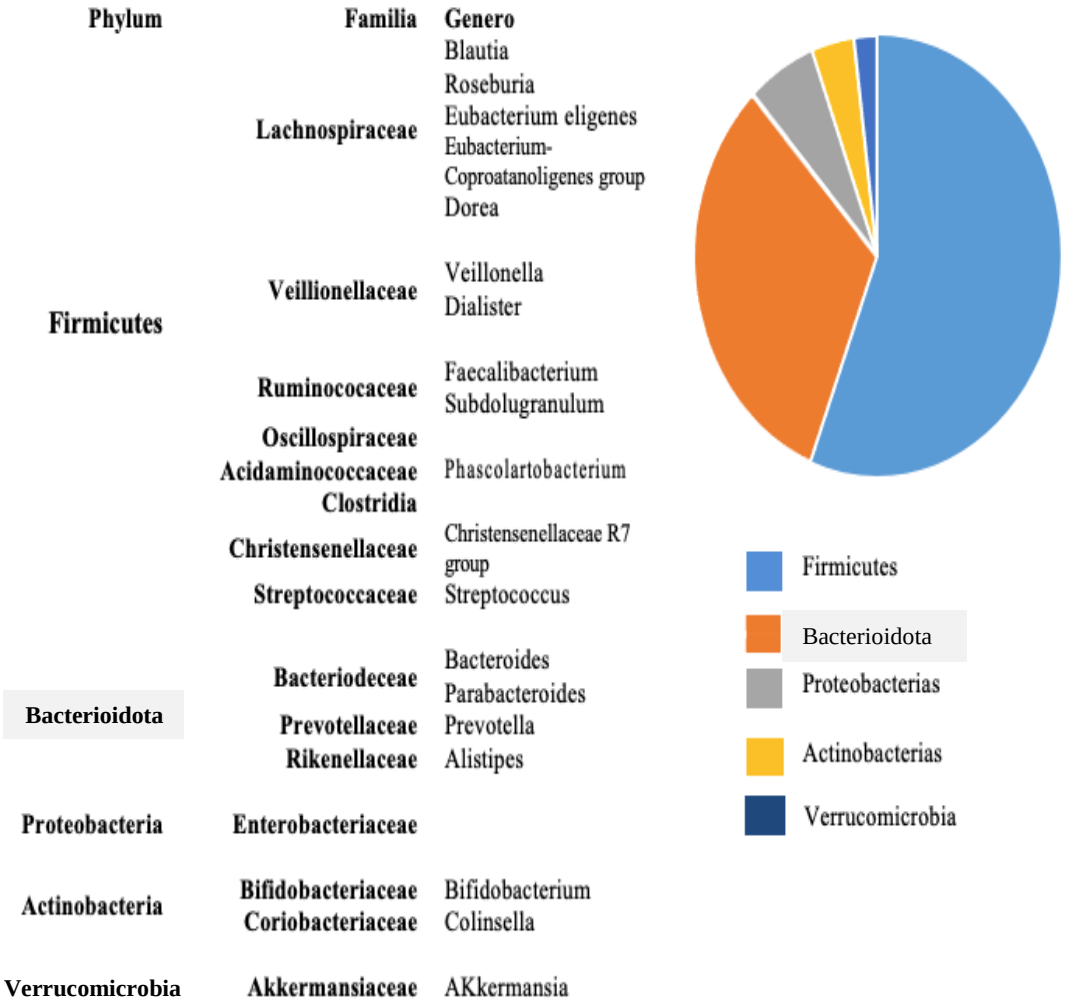
Table 2. Cambio de macro y micronutrientes durante la intervención.

		FAWGT Diet n=17				UD n=12				
		Basal	RIQ	Final	RIQ	Basal	IQR	UD	RIQ	p value
Kcal		1774	216	1660	325	1877,50	297,50	1800	242,80	0,006
P	%	16,70	3,15	16,40	3,9	17,50	3,55	17	3,65	0,747
CHO	%	51,90	6,85	54,80	8,5	52,90	4,70	54	1,52	0,14
Fibra	g/d	13,00	5,60	34,15	12,16	14,10	4,18	15	3,45	<0,001
Grasa	%	31,10	4,80	29,80	6,10	29,70	3,53	29,15	4,40	0,184
AGS	%	9,97	5,05	7,25	1,93	11,47	2,44	10,9	1,75	<0,001
AGMI	%	10,78	4,03	12,44	2,94	9,28	1,69	9	3,27	<0,001
AGPI	%	6,98	4,06	6,35	1,67	4,77	1,27	4,42	1,17	<0,001
Omega 6	g	11,56	5,26	10,13	3,49	8,23	3,91	7,31	1,36	0,002
Omega 3	g	0,96	0,35	1,50	0,90	0,90	0,28	0,8	0,15	0,002
ω3/ω6 ratio		12,04	3,47	6,64	3,72	9,53	2,10	9,45	1,49	0,002
Colesterol	mg	306,40	119,63	257,33	189,6	307,84	158,6	326	137,3	<0,001
βcarotenos	mcg	2442	2176	7394	4130	1461	2373	1775	1731	0,156
Vitamin C	mg	77,00	100,70	188,24	88,04	102,87	94,13	107,8	62,25	<0,001
Vitamin E	mg	4,66	2,20	6,80	2,99	3,95	1,50	3,45	1,18	<0,001
Fólato	mcg	267,96	174,50	301,64	134,20	239,47	126,4	285	186,80	0.363
Magnesio	mg	197,93	81,10	296,75	65,37	228,71	94,02	226	53,50	<0,001
Zinc	mg	8,03	3,98	7,42	2,36	8,51	4,32	9	4,88	0.198
Selenio	mcg	78,85	22,41	68,23	13,08	85,31	28,87	82	15,88	0,001

Los valores están expresados como mediana y rango interquartil (RIQ). FAWGT: diet compuesta por frutas, verduras, aguacate, granos enteros y trucha; UD: usual diet; AGS: ácidos grasos saturados; AGMI: ácidos grasos monoinsaturados; AGPI: ácidos grasos poliinsaturados. Las variables fueron calculadas usando pruebas no paramétricas (Kruskal Wallis).

Composición de la microbiota en la población de estudio Patrón Global

La caracterización filogenética de todas las muestras muestra los 3 Phylum principales en las siguientes proporciones: Firmicutes (56 %), Bacteroidota (32%), Proteobacteria (6 %) y una menor abundancia de: Actinobacteria (4%) y Verrucomicrobia (2 %). Los taxones más abundantes fueron: *Subduligranulum* (21.0%), *Roseburia (20%), Eubacterium coprostanoligenes group* (12%), *Alistipes* (10%), *Dialister* (7 %), *Vellionella* (5%), *Phascolartobacterium* (4%), *Streptococcus (4%), Bifidobacterium* (2 %), *Blautia* (2 %) *y Arkkermansia* (2%). **Figura 2.**



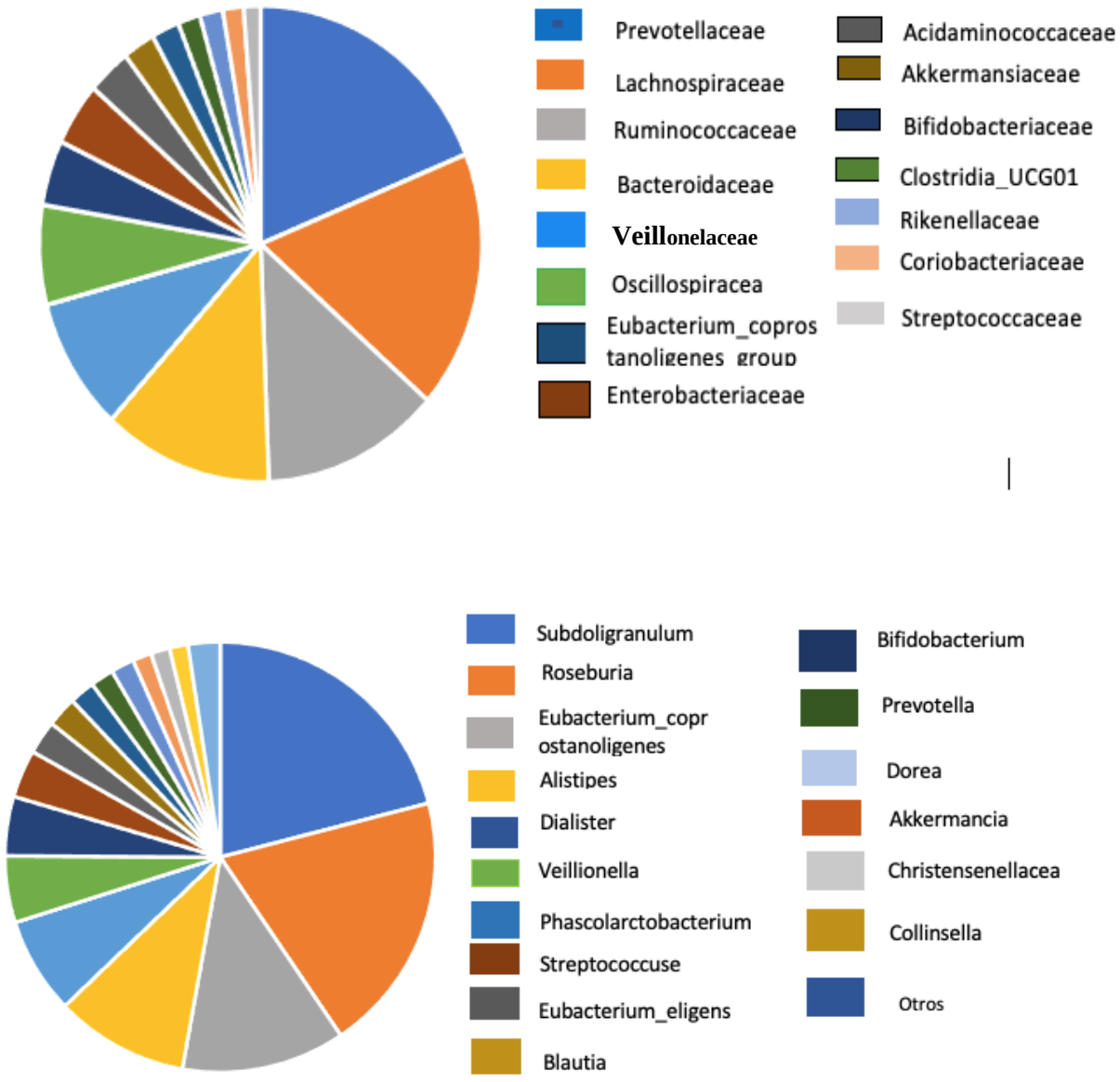


Figura 2. Composición general de la microbiota intestinal de las 29 participantes.

Alfa y beta Diversidad.

Las muestras de las diferentes dietas después de 8 semanas mostraron número similares en los 3 índices para determinar la α diversidad (p >0,05), fueron analizadas por pruebas no paramétricas.

Cambios en taxones específicos a nivel de genero

Se observó una disminución de la abundancia relativa del género Roseburia en la UD comparado con la dieta FAWGT (p=0.031) y una disminución de la familia Vellionellaceae con la dieta FAWGT (p=0.024). **Figura 3**

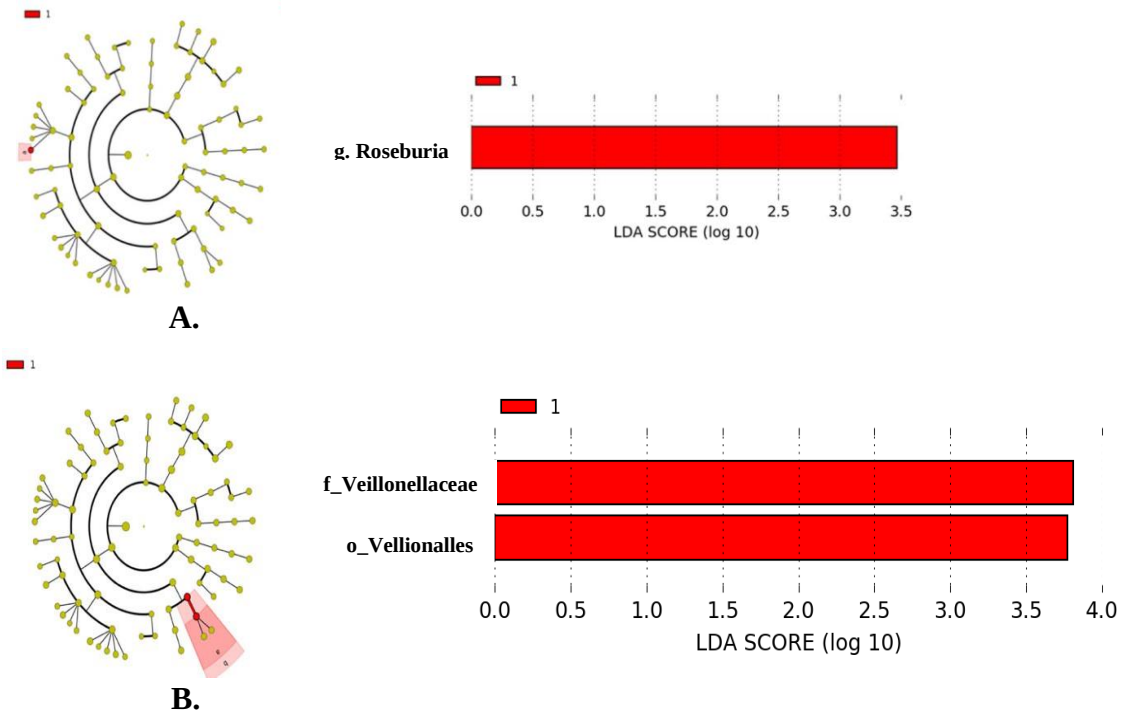


Figura 3. Gráfico LEfSe. A. Genero Roseburia B. Familia Veillonellaceae; Orden Vellionellales

Relación entre variables antropométricas y metabólicas con la microbiota intestinal.

Se encontró una relación positiva entre la abundancia relativa de Firmicutes y el IMC; (r=0.517, p=0.034); igualmente con los niveles de insulina (r=0,480 p=0,05). A nivel de genero se encontró una relación positiva entre el género Veillionella con el peso y el Índice cintura cadera (ICC) (r=0,647 p=0,005 y r=0,495 p=0,043 respectivamente); del género Subduligranulum (r=0,640 p=0,006) y una relación negativa entre los niveles de colesterol total y colesterol LDL con la abundancia relativa del género Bifidobacterium (r=-0,533 p=0,028 y r=-0,568 p=0,037 respectivamente), también una relación negativa entre los niveles de colesterol HDL con el género Collinsella (r=-0,503 p=0,039); igualmente entre los niveles

de colesterol total y triglicéridos con el género Butyricicocus (r=-0.494, p=0.044; r=-0.548, p=0.023 respectivamente). Estas relaciones se encontraron solo con la dieta FAWGT. Tabla 3.

Tabla3. Correlaciones entre géneros bacterianos y variables antropométricas y bioquímicas con la dieta FAWGT

	Peso	IMC	ICC	Insulina	CT	c-HDL	c-LDL	TG
p. Firmicutes	-0,042	**0,517**	0,304	**0,480**	-0,462	-0,112	-0,304	-0,159
g. Veillonella	**-0,647**	-0,205	**-0,495**	**-0,073**	-0,241	0,211	-0,274	0,129
g. Subduligranulum	-0,040	0,273	0,106	**0,640**	-0,011	0,007	-0,018	-0,055
g. Bifidobacterium	-0,107	0,265	0,383	0,234	**-0,533**	0,091	**-0,508**	-0,414
g. Colinsella	0,416	0,269	**0,601**	0,278	-0,140	**-0,503**	-0,065	-0,05
g. Butyricicocus	-0,093	0,108	0,295	-0,044	**-0,494**	0,153	-0,430	**-0,548**

Discusión

En el presente estudio, se caracterizó la microbiota intestinal de 29 mujeres colombianas con obesidad y se evaluaron los cambios generados por el consumo de la dieta FAWGT, en comparación con la UD, durante 8 semanas. La composición inicial de la MI se caracterizó por la presencia mayoritaria de los Phylum Firmicutes, y Bacteriodota en proporciones de 56 y 32% respectivamente. Después de 8 semanas de intervención se encontró una disminución de la abundancia relativa de la familia *Veillonellaceae* y del orden *Vellionalles* con la dieta FAWGT y una disminución del género *Roseburia* después de la dieta usual, no se encontraron cambios significativos en los parámetros clínicos al comparar los dos grupos.

Una revisión sistemática que incluyó 60 estudios de casos y controles, encontró que el p_Firmicutes y sus familias Lachnospiraceae y Megasphaera, así como Escherichia perteneciente al p_Proteobacteria se asociaron a la obesidad en las personas con obesidad. A nivel de género, las asociaciones fueron diferentes dependiendo de la ubicación geográfica de los estudios (oriente u occidente). Prevotella y Ruminococcus se asociaron a la obesidad en Occidente y a normopeso en Oriente. Roseburia y Bifidobacterium se asociaron a la obesidad solo en Oriente y Lactobacillus en Occidente (16). Otro metaanálisis encontró una mayor abundancia relativa de los géneros: Acidaminococcus, Dialister, Dorea, Escherichia-Shigella, Eubacterium, Fusobacterium, Megasphera, Prevotella, Roseburia, Streptococcus, entre otros, en personas obesas en comparación con personas con normopeso (17) .

En nuestro estudio el p_Firmicutes se correlacionó positivamente con el IMC (r=0,517 p=0,034). La familia Lachnospiraceae y Ruminococcaceae fueron las más abundantes (18 y 13% respectivamente), pertenecientes al p_Firmicutes y del p_Bacteriodota el más abundante fue el género Prevotella (19 %). Nuestros resultados coinciden con el hallazgo hecho por Palmas et al, quienes en una población italiana con sobrepeso y obesidad, encontraron un predominio de la familia Lachnospiraceae (18). En esta familia se encuentran los principales géneros productores de ácidos grasos de cadena corta (AGCC) principalmente acetato, propionato y butirato, que se ha reportado tienen un efecto benéfico sobre la salud humana. Sin embargo, en la obesidad el incremento de su abundancia podría asociarse con enfermedades metabólicas probablemente por la producción de AGCC diferentes al butirato (19).

El cambio en taxones específicos, en el presente estudio, se evidenció con la disminución del g. Roseburia y de la f. Vellionellaceae, después de 8 semanas de intervención, con la UD y con la dieta FAWGT respectivamente. Nuestros resultados coinciden parcialmente con otros estudios. Haro et al, compararon el consumo de una dieta baja en grasa y alta en carbohidratos complejos, con una dieta mediterránea (DM), ambas saludables, con la primera se incrementó el género Prevotella y disminuyo el género Roseburia, mientras que con una DM disminuyó el g. Prevotella y aumento el g. Roseburia (20) . Este último, se caracteriza por la producción de butirato que juega un papel importante en el mantenimiento de la salud intestinal (21) . En pacientes con Diabetes Mellitus tipo 2, este género, se ha encontrado disminuido por lo que el consumo de una DM podría tener un efecto protector frente al desarrollo de esta enfermedad (22) . El reemplazo de un patrón de dieta occidental por un patrón de DM, incremento la abundancia relativa de Faecalibacterium praustnizii, perteneciente a la familia Ruminocococeae y al p_Firmicutes, degradador de fibra y productor de AGCC. La adherencia a la DM se ha asociado con un incremento en la producción de AGCC (23). En este sentido, una intervención de 8 semanas con DM, mostró mayores niveles de butirato postprandial y este correlacionó negativamente con los niveles de insulina. (24). El ácido butírico podría desempeñar un papel clave en la regulación del metabolismo de la glucosa actuando a nivel de secreción de la insulina o de la sensibilidad a la insulina, ya que activa la proteína G

acoplada a receptores (GPCR) en el intestino con producción del péptido 1 similar al glucagón (GLP-1), aumentando la secreción de insulina. Además, podría disminuir el depósito ectópico de lípidos y la inflamación en el hígado y tejidos periféricos, a través de un aumento en la Beta oxidación de los ácidos grasos (25,26) .

En nuestro estudio con la dieta FAWGT disminuyó el orden Vellionalles y la familia Veillonellaceae, este hallazgo es coherente con un modelo de regresión predictivo de inflamación de bajo grado, basado en la composición de la microbiota, en donde se encontró que familias como: Enterobacteriaceae, Prevotellaceae, Veillonellaceae entre otras, fueron más abundantes en sujetos con un mayor índice inflamatorio relacionado con la obesidad (27).

En el presente estudio se encontró una correlación negativa entre el g. Bifidobacterium y los niveles de CT y cLDL, similar a lo encontrado por Dengfeng Xu et al, en una población china después de una dieta basada en avena, en comparación con el consumo de arroz (28). En el presente estudio las participantes con la dieta FAWGT consumieron 115 g/d de cereales integrales que incluyo arepa, arroz y avena principalmente. EL g. Colinsella se correlacionó de manera positiva con el índice cintura cadera y negativamente con el cHDL (r=0,601; r=-0,503 respectivamente). Estos resultados coinciden parcialmente con un estudio transversal, realizado en población española, en donde se identificaron como marcadores de obesidad las siguientes bacterias: Dorea formicigenerans, Dorea longicatena y Collinsella aerofaciens (29).

En este estudio el género Roseburia no aumento con la dieta FAWGT, su abundancia relativa se mantuvo posiblemente por el aumento en el consumo de omega 3, Vitamina C y Vitamina E, cuya fuente fueron alimentos como: trucha 280g/semana y frutas y verduras 680g/d. No se identificaron cambios en la diversidad alfa y beta. Kopf et al, encontraron cambios en la diversidad alfa con un aumento en el consumo de frutas y verduras en comparación con el consumo de granos enteros y un grupo control, sin diferencias a nivel de phylum o género (30). Se requieren más estudios con mayor duración y tamaño de muestra para obtener resultados mas contundentes.

La dieta FAWGT no modifico la diversidad α y β de la microbiota intestinal de mujeres con

obesidad al compararla con la dieta usual. Se encontró una disminución de la familia *Vellionellaceae* con esta dieta suplementada con frutas, verduras, aguacate, granos enteros y trucha, igualmente del género *Roseburia* con la dieta habitual de las participantes. Estos resultados podrían conferirle a esta dieta un factor protector para el mantenimiento de géneros productores de butirato, al que se le atribuyen beneficios para mejorar la respuesta inmune y metabólica sistémica.

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CAPITULO VI: DISCUSIÓN

El objetivo de este estudio fue evaluar el efecto del consumo de una dieta FAWGT, durante 8 semanas, sobre la lipemia, la insulinemia, la expresión de genes proinflamatorios, de estrés oxidativo en estado postprandial y la microbiota intestinal en personas con obesidad, como una alternativa viable y culturalmente aceptada por la población de la region central de Colombia.

El consumo de la dieta FAWGT durante 8 semanas condujo a un menor incremento de los niveles de triglicéridos, cVLDL e insulina postprandial en comparación con la dieta usual y a una disminución de la resistencia a la insulina en personas con obesidad, sin una pérdida de peso clínicamente significativa (45). También, mostró una disminución postprandial en la expresión de genes proinflamatorios (*NFKB1, IL6, IL1β*) y de estrés oxidativo (*NFE2L2*) y una correlación positiva entre la expresión de los genes *NFkB1* e *IL1β* con los niveles de triglicéridos y de insulina con la dieta FAWGT y la dieta usual respectivamente (41).

Por último, con el consumo de este patrón dietario disminuyó la abundancia relativa del orden Vellionellales y familia Veillonellaceae con la dieta FAWGT y del género Roseburia con la dieta usual. Se encontró una relación positiva entre el IMC y la abundancia relativa de Firmicutes (r=0.517, p=0.034); A nivel de genero se encontró una relación positiva entre el género Veillonella con el peso y el ICC (r=0,647 p=0,005 y r=0,495 p=0,043 respectivamente); los niveles séricos de insulina mostraron una relación positiva con el Phylum Firmicutes (r=0,480 p=0,05) y con el género Subduligranulum (r=0,640 p=0,006).

Se encontró una relación negativa entre los niveles de Colesterol total y Colesterol LDL con la abundancia relativa del género Bifidobacterium (r=-0,533 p=0,028 y r=-0,568 p=0,037 respectivamente) y de los niveles séricos de Colesterol HDL con el género Collinsella (r=-0,503 p=0,039); igualmente una relación negativa entre los niveles de Colesterol Total y Triglicéridos con el género Butyricicocus (r=-0.494, p=0.044; r=-0.548, p=0.023 respectivamente.

Estos cambios estuvieron probablemente soportados por un incremento en la ingesta de ácidos grasos saludables como: ácidos grasos monoinsaturados de 10,78 a 12,44% y la disminución de AGS de 9,97% a 7,25% de la energía total; igualmente, por un aumento de la ingesta de fibra de 13 a 34,15 g/d, Vitamina C y E de 77 a 188 mg y de 4,66 mg a 6,8 mg respectivamente.

Algunos alimentos que se consideraron claves fueron suministrados a los participantes y constituyeron la fuente principal de los nutrientes mencionados. Los alimentos más consumidos con la dieta FAWGT fueron: frutas 478 g/d (mango, naranja, granadilla, manzana, mandarina, piña, papaya y chontaduro); verduras 207 g/d (tomate, zanahoria, lechuga, cebolla y habichuela); aguacate 18 g/d; cereales integrales 115 g/d (arepa, arroz) y trucha 41g/d.

Varios estudios muestran que patrones alimentarios saludables como, la dieta mediterránea, mejora los niveles de lípidos en estado postprandial (46). Se ha sugerido que este efecto podría atribuirse al consumo de MUFAs presentes en el aceite de oliva, al disminuir la glucosa, la insulina y el péptido 1 similar al glucagón (GLP1), este actúa mejorando la secreción de la insulina y la proliferación de células β pancreáticas en estado postprandial, en comparación con una dieta rica en carbohidratos. (47). Otro estudio muestra que una ingesta de 20% de MUFA, ocasionan un incremento temprano de TG y, a la vez, un aclaramiento más rápido de los mismos, en comparación con dietas ricas es AGS o bajas en grasa (48). En nuestro estudio, un menor incremento de TG y de cVLDL, después de la ingesta de la dieta FAWGT, podría atribuírse a un aumento en el consumo de MUFA de 10,8 a 12,4 % cuya fuente principal fue el aguacate (18 g/d). Estos hallazgos son similares a los reportados por Anderson-Vásquez HE et al, en los cuales, la adición de 250 g de aguacate a una dieta usual, disminuyó los niveles de Colesterol LDL y TG (49). Igualmente, en nuestro estudio se redujo la relación omega 6/omega 3 de 12:1 a 6:1, posiblemente debido al consumo de 280 g/semana de trucha. Tanto los MUFA como el omega 3 tienen efectos sobre la lipemia y la insulinemia postprandial (50).

La dieta FAWGT se caracterizó por el consumo de trucha, que contiene 1,4 g de omega 3 (280 mg de ácido eicopentaenoico (EPA) y 160 mg de ácido docosahexaenoico (DHA) por cada 100 g) además, otros nutrientes como selenio y vitamina D, entre otros (51). El ácido graso omega 3 puede actuar como ligando del receptor activador del proliferador del peroxisoma γ (PPAR γ), un factor de transcripción que regula genes involucrados con el metabolismo de lípidos, almacenamiento de grasa, función del adipocito y acción de la insulina (52). El DHA inhibe el efecto sinérgico entre el ácido palmítico y el lipopolisacárido (LPS) sobre la expresión de genes proinflamatorios, vía activación del factor de transcripción NF-κB (53). En este sentido, otro estudio in vitro muestra que el consumo de aguacate disminuye la concentración de moléculas proinflamatorias como la IL1β, IL6 y el factor de necrosis tumoral α a través de la modulación del factor NF-κB (54) .

Otro nutriente a tener en cuenta fue la fibra. Un aumento en el consumo de fibra ha mostrado efectos beneficos sobre la salud. El reemplazo de granos refinados por granos enteros, con un consumo de 40 g de fibra, disminuyó los niveles de insulina sin disminución paralela de la glucosa sanguinea (55). Sun et, al evidenciaron una disminución de la insulina postprandial al combinar 50 g de carbohidratos con bajo índice glicémico y 40 g de ácidos grasos (SFA; MUFA o PUFA), esta disminución se dio independiente del tipo de ácido graso (56). En este contexto, la contribución de nuestro estudio sugiere que el consumo de arepa integral, arroz integral y avena de 115 g/d constituyó un incremento de 32 g en el consumo de fibra que fue mayor que en la dieta usual con solo 15 g. Este efecto podría deberse a que la fibra es metabolizada por la microbiota intestinal produciendo ácidos grasos de cadena corta principalmente propionato y butirato que mejoran la sensibilidad a la insulina (57). El aumento de fibra con este modelo dietario, podría también reducir el riesgo cardiovascular a través de la reducción de la resistencia a la insulina (HOMA-IR), como lo describen Sasso y colaboradores (58).

El consumo de frutas se ha asociado con un incremento en la capacidad antioxidante, aumentando el potencial de eliminar las especies de oxígeno reactivo, las cuales se encuentran aumentadas en personas con obesidad (59). La vitamina C y E disminuyen el daño oxidativo inhibiendo la peroxidación lipídica y manteniendo la funcionalidad de las

células Beta pancreáticas, que inhiben la gluconeogénesis y la glucogenólisis (60). Igualmente, la vitamina C incrementa la acción de la lipoproteína lipasa en el tejido adiposo y disminuye los TG, VLDL y LDL colesterol (61) . Un estudio mostró, que un complejo multivitamínico rico en β carotenos, Vitamina C y tocopherol disminuyó la producción de citoquinas proinflamatorias IL6 y TNFα e incrementó la de IL4, antiinflamatoria, en células mononucleares de personas diabeticas (62). La ingesta diaria de 400 g/d de frutas enteras(banano, mandarina, manzana, fresa, naranja, durazno y mango) durante 14 días en jóvenes colombianos entre 18 y 30 años indujo una reducción en la expresión de los genes *RELA* e *IL6R* y un aumento en las concentraciones de colesterol HDL en comparación con un grupo control (63). Estos resultados son similares a los obtenidos en nuestro estudio, en donde los participantes consumieron 680g/d entre frutas y verduras, con una ingesta final de Vit. C y E de 207,13 mg y de 7,01 mg respectivamente. Las principales fuentes de estas vitaminas fueron frutas disponibles en la región cafetera de Colombia como mango, naranja, maracuyá y chontaduro, ricas en Vit. C, E y compuestos fenólicos con poder antioxidante (β carotenos y tocopherol) (64), lo que posiblemente indujo la reducción de la expresión de genes como: *IL6, IL1β, NFKB1y NFE2L2* en estado postprandial (41).

El gen *NFE2L2* codifica el factor de transcripción NRF2, que regula la transcripción de genes relacionados con la respuesta al estrés oxidativo, el cual esta directamente asociado a la respuesta inflamatoria (65). En este sentido, nuestro trabajo mostró una reducción posprandial en la expresión del gen *NFE2L2* con la dieta FAWGT, mientras que el consumo de la UD tuvo el efecto contrario. Estos hallazgos sugieren un efecto benéfico de esta dieta sobre la inflamación y la respuesta al estrés oxidativo, lo que posiblemente se debe a una sinergia entre los principales alimentos que constituyen el modelo dietético, incluidos los ácidos grasos saludables de origen animal y vegetal y las frutas locales, entre otros.

Nuestro estudio tuvo un enfoque nutrigenómico, que se basó en el hecho de que los nutrientes y los compuestos bioactivos de la dieta pueden modificar la expresión génica. El descubrimiento de estas interacciones gen-nutriente ayudará al uso de dietas personalizadas. En línea con lo anterior, este conocimiento puede permitir el diseño de estrategias dietéticas centradas en la reducción de la expresión de genes inflamatorios o de estrés oxidativo, lo cual

es especialmente importante en el caso de enfermedades no transmisibles como la obesidad, consideradas actualmente un importante problema de salud pública mundial (9). De hecho, estudios anteriores han demostrado el efecto de la dieta o de sus componentes sobre los mecanismos moleculares asociados a la actividad inflamatoria y al estrés oxidativo . Un estudio demostró que el uso de un modelo de dieta mediterránea inducía la regulación a la baja de los genes proinflamatorios y de estrés del retículo endoplásmico, incluso tras la suplementación con coenzima Q10, frente a un modelo de dieta rica en grasas saturadas (66). Además, la dieta nórdica demostró que este modelo reducía en tejido adiposo subcutáneo, genes inflamatorios como *IRF1, CD67, IL-32 e IL6R* en comparación con una dieta control (67). En otro estudio, este mismo patrón dietario, indujo una menor expresión postprandial de genes proinflamatorios como *TLR4, IL18 y CD36* e incrementó la expresión del gen PPARD, antiinflamatorio, en comparación con una dieta de control, en una población con síndrome metabólico (27), lo que demuestra, al igual que en nuestro estudio, que el consumo de patrones dietéticos saludables tiene un impacto beneficioso en el perfil de expresión génica.

En el presente estudio, la disminución de la expresión postprandial de los genes proinflamatorios (*NFKB1*, *IL6 e IL1β*) podría deberse a que el gen *NFKB1* codifica para la proteína p50, una subunidad del factor de transcripción NF-kB, que activa la transcripción de los genes que activa la transcripción de genes proinflamatorios (*TNF-α, IL1β, IL6,* entre otros), que regulan la respuesta inflamatoria (68). La disminución de la expresión postprandial de *IL6* e *IL1β* tras 8 semanas de intervención con la dieta FAWGT podría estar asociada a la menor activación de la vía de señalización del factor de transcripción NF-kB inducida por la ingesta de ácidos grasos saludables procedentes de la trucha y el aguacate (omega 3, MUFA y PUFA), que también mejora los niveles postprandiales de triglicéridos y la homeostasis de la glucosa (69,70).

La dieta FAWGT se basó en el consumo de alimentos típicos de la región como: arepa, arroz, avena, lentejas, tomate, zanahoria, lechuga, cebolla, frijoles, aguacate, trucha, mango, naranja, manzana, pera, mandarina, piña, papaya, chontaduro, uchuva, carambolo y granadilla, todos juntos aportaron fibra, antioxidantes, vitaminas y MUFA en diferentes

proporciones. Es complejo discernir cual componente específico direccionó las diferencias encontradas entre la dieta FAWGT y la UD, probablemente sea el resultado de una sinergia entre estos alimentos. Así, las características de la dieta FAWGT dan cuenta de una reducción del estado inflamatorio, como sugiere la disminución de la expresión de genes proinflamatorios y de estrés oxidativo que se muestran en este trabajo.

Limitaciones

Una de las limitaciones de este trabajo fue el tamaño de la muestra, no obstante, el diseño del estudio nos permitió detectar el efecto neto de la intervención con grupos pequeños. La duración de la intervención pudo ser otra limitante, posiblemente se podrían detectar efectos adicionales con intervenciones más prolongadas.

Otra limitación fue que no se determinó el nivel de proteínas derivadas de los cambios en la expresión génica, lo que nos impidió relacionar estos dos componentes. Siendo asi, se sugiere ampliar este estudio para confirmar nuestros hallazgos.

Una de las fortalezas de nuestro estudio fue el diseño; aleatorizado, cruzado, que reduce la variación interindividual, lo que nos permitió obtener evidencia científica confiable. Adicionalmente la buena adherencia de los pacientes y el el seguimiento estrecho y riguroso que se le dió a los participantes.

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CAPITULO VII: CONCLUSIONES GENERALES Y RECOMENDACIONES

Conclusiones

1. Una característica común de distintas intervenciones, identificadas en la revisión sistemática, es que incluyen dietas mixtas siendo un enfoque prometedor para reducir los marcadores inflamatorios y de disfunción endotelial. En este sentido, para aumentar la adherencia a patrones dietéticos saludables, es importante proporcionar una dieta variada y adecuada a los alimentos disponibles en cada región.

2. La ingesta de una comida rica en carbohidratos complejos y grasas polinsaturadas no disminuyó la lipemia postprandial al compararla con una comida rica en grasas saturadas y carbohidratos simples, posiblemente debido a una ingesta insuficiente de ácidos grasos monoinsaturados y polifenoles.

3. El consumo de una dieta rica en frutas y verduras, avocado, granos enteros y trucha puede ser considerada una alternativa válida a otras dietas cardiosaludables ya que mejora los niveles de insulinemia y lipemia postprandial en personas con obesidad, sin causar una pérdida de peso clínicamente significativa.

4. Este patrón dietario , reduce el estado inflamatorio postprandial debido a que mejora la regulación molecular de genes involucrados en la respuesta inflamatoria y en estrés oxidativo mostrando un efecto benéfico similar a modelos saludables.

5. La dieta FAWGT no modificó la diversidad α y β en la microbiota intestinal de mujeres con obesidad al compararla con la dieta usual. Se encontró una disminución de la familia *Vellionellaceae* con la dieta FAWGT y del género *Roseburia* con la dieta usual, estos resultados podrían conferirle a esta dieta un factor protector para el mantenimiento de géneros productores de butirato al que se le atribuyen beneficios para mejorar la respuesta inmune y metabólica sistémica.

Recomendaciones

Como resultado de esta tesis de doctorado, a continuación, se presentan algunas recomendaciones que se consideran pertinentes para futuros estudios:

Aumentar la duración de las intervenciones, a pesar de que existe evidencia de cambios a corto plazo, quizás se obtendrían resultados más contundentes.

Medir marcadores en sangre, que permitan evidenciar la adherencia al consumo de alimentos específicos, lo cual ayudaría a corroborar la información suministrada por los participantes a través de los recordatorios de 24 horas o cuestionarios de frecuencia de consumo.

Promover el consumo de esta dieta en el eje cafetero, a través de la socialización de los resultados de este estudio, e intentar incidir en políticas públicas de prevención, que conduzcan a disminuir la incidencia de la obesidad y de ECNT.

Realizar estudios que relacionen la nutrigenómica, la nutrigenética y el microbioma intestinal con la dieta para encontrar marcadores predictivos de distintas patologías relacionadas con la inflamación crónica de bajo grado y el estrés oxidativo.

Realizar estudios similares en otras zonas del país donde la diversidad de alimentos y hábitos alimenatarios varían sustancialmente con relación a los de la región cafetera.

ACTIVIDADES COMPLEMENTARIAS DURANTE LA FORMACION DOCTORAL

Durante la formación doctoral se realizaron varios cursos, un diplomado, una pasantía nacional y dos pasantías internacionales.

CURSOS

- Programa Análisis por Transcriptómica en la Universidad EAFIT con una duración de 20horas.
- Programa de Capacitación en Escritura Académica y Presentaciones Orales en Contextos Académicos.Realizado con la Maestría en Ingles de la Universidad de Caldas con una duraciónde 60 horas.

DIPLOMADO

- Diplomado en Bioestadística para no Estadísticos, mediado por SPSS con el Departamento de Salud Pública de la Universidad de Caldas.

PASANTÍA NACIONAL

Se realizo una pasantía en el Instituto Tecnológico Metropolitano en la ciudad de Medellín, con el Grupo de Investigación e Innovación Biomédica GI2B. Esta pasantía tuvo como objetivo la estandarización de métodos de extracción de ARN y Proteínas a partir de células mononucleares de sangre periférica, con una duración de 10 días.

PASANTIAS INTERNACIONALES

- Pasantía en la Universidad de Guadalajara
- Pasantía en el Instituto Maimónides de Investigación Biomédica de Córdoba(IMIBIC).

ANEXOS

Anexo 1. Aprobación del protocolo de investigación por el comité de ética de la Universidad de Caldas

UNIVERSIDAD DE CALDAS
FACULTAD DE CIENCIAS PARA LA SALUD
COMITÉ DE BIOÉTICA

FECHA	17 de Mayo de 2017
CONSECUTIVO	CBCS-023

Nombre del Investigador	Clara Helena González Diana María Muñoz
Facultad	Ciencias de la Salud
Doctorado	Ciencias Biomédicas
Proyecto de Investigación:	Regulación de la metainflamación por una dieta con componentes antiinflamatorios en adultos con sobrepeso y obesidad

EVALUACIÓN:

Se considera una investigación **con RIESGO MÍNIMO**, de acuerdo a la Resolución 8430 de 1993 del Ministerio de Salud.

CONSIDERACIONES:

Los investigadores deben tener en cuenta que si existen cambios en la formulación del proyecto o las condiciones de los sujetos investigados (Consentimiento Informado), esto debe ser informado a este Comité.

El Comité podrá solicitar información posterior sobre el desarrollo del proyecto y los cambios de acuerdo a las recomendaciones establecidas.

ACTA No 009 de 2017
SE APRUEBA (x)
SE APRUEBA CON RECOMENDACIONES ( )
NO SE APRUEBA ( )

NATALIA GARCIA RESTREPO
Presidente

Anexo 2. Aprobación del protocolo de investigación por el comité de ética de la Clínica Comfamiliar Pereira.

Comfamiliar
RISARALDA

3014

EL COMITÉ DE ÉTICA E INVESTIGACIÓN EN SALUD DE LA CLINICA COMFAMILIAR RISARALDA

Certifica que:

La Dra. **DIANA MARIA MUÑOZ**, el día 5 de JULIO de 2016, presentó el proyecto de investigación: "EFECTO DE UNA DIETA ANTIINFLAMATORIA SOBRE LA EXPRESIÓN GÉNICA POSPTPRANDIAL EN MONONUCLEARES DE MUJERES ADULTAS OBESAS".

El comité considera que la realización del proyecto tiene un riesgo mínimo de acuerdo a lo establecido por la resolución 8430 de 1993 autoriza su ejecución con las siguientes recomendaciones:

- ✓ Aclarar dentro de la metodología dentro de los criterios de inclusión si trabajará con pacientes obesas o con sobrepeso, y rectificar si trabajará con un IMC de 25 o 30
- ✓ Se requiere un consentimiento informado claro donde se especifique que la dieta puede aumentar o disminuir el peso de las pacientes.
- ✓ Aclarar en el proyecto cuáles serían las dos dietas, hacerlo más explícito.
- ✓ Cuantificar el presupuesto de acuerdo al uso de los equipos de los laboratorios de Comfamiliar.
- ✓ Enviar al correo de investigación el consentimiento informado que será utilizado en la investigación.

Una vez realizado los cambios en el proyecto por favor enviar una copia al correo del comité de ética e investigación en salud para el aval definitivo

Lo anterior se firma el día 7 de julio de 2016

GLORIA LILIANA PORRAS H.
Presidente

HECTOR ALEJANDRO SALAZAR
Secretario

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E - mail: comiteeti@comfamiliar.com - visítanos en www.comfamiliar.com

Anexo 3. Hoja de información del consentimiento informado

FO**RMATO 1. HOJA INFORMACION CONSENTIMIENTO INFORMADO**

Consentimiento Informado – Proyecto De Investigación: "Efecto de una dieta antiinflamatoria sobre la expresión génica postprandial en mononucleares de adultos con obesidad"

Estimado(a) señor (a): El grupo de Bioimpedancia electrica, el grupo de Nutrición, seguridad alimentaria y metabolismo de la Universidad de Caldas en alianza con el grupo de Gerencia del cuidado de la Universidad Libre seccional Pereira y la Clínica Comfamiliar Pereira han decidido buscar alternativas para la prevención y el manejo del sobrepeso y la obesidad, dos enfermedades que afectan a la mitad de nuestra población adulta. Es por esto que estamos invitándolo a participar voluntariamente en un proyecto de investigación que busca indagar en los efectos que pueden tener la alimentación en su organismo, permitiendo en un futuro convertir la alimentación en una potente herramienta para reducir el riesgo de adquirir enfermedad. Para ello deseamos evaluar los efectos de dos tipos de alimentación: uno basada en productos naturales (disponibles en nuestra región) y el habitual de la región, sobre distintas variables involucradas en procesos inflamatorios que se relacionan con las enfermedades ocasionadas por el sobrepeso y la obesidad. El proyecto cuenta con el aval del Comité de Ética y será llevado a cabo por profesores universitarios capacitados para su ejecución.

Se le proporcionara un plan alimentario dirigido, ninguno de ellos ocasionara aumento de peso, durante 8 semanas con cada uno de los tipos de alimentación, se tomarán medidas corporales (Peso talla etc.) ; muestras de materia fecal y sangre en distintos momentos, al inicio y al final del estudio. El programa se iniciará con un grupo de voluntarios a quienes les realizaremos las pruebas descritas en la tabla anexa, y con lo que usted podrá obtener el resultado del estado nutricional, condición física, y composición corporal. Las pruebas están clasificadas como de riesgo mínimo.

Sin embargo, en caso de presentarse problemas en su salud, usted deberá acudir, como es lo habitual a la EPS a la que se encuentra afiliado.

Igualmente, durante el tiempo del proyecto, usted está autorizado para comunicarse con los responsables del proyecto a cualquier hora del día o la noche, en caso de necesitar asesoría con respecto a su alimentación.

Metodología: El día del estudio debe estar en ayunas y permanecer toda la mañana en el sitio donde se tomarán las muestras. Se llevan a cabo extracciones de sangre en ayuno, y 4 horas después de la ingesta de un desayuno.

Tabla Valoración del estado nutricional

Mediciones	Resultados
Peso (con una balanza) y estatura (Con un estadiómetro)	Índice de masa corporal
Medición de pliegues de grasa subcutáneos según Durnin and Womersley	Porcentaje de grasa corporal
Extracción de muestras de sangre. Puede presentar dolor momentáneo y la posibilidad de un pequeño hematoma (moretón).	Pruebas bioquímicas y de expresión génica.
Encuesta nutricional	Valoración de ingesta de macro y micronutrientes.

- ✓ Aseguraremos su comodidad, bienestar y seguridad.
- ✓ Las mediciones se realizan en ropa comoda con una bata hospitalaria y un par de medias desechables.
- ✓ Durante las pruebas de laboratorio estarán presentes una bacterióloga o médica o enfermera, responsables del estudio.
- ✓ Usted deberá diligenciar una encuesta diaria del consumo de alimentos.
- ✓ Usted se reserva el derecho a retirarse en cualquier momento, sin necesidad de explicación, si así lo desea.
- ✓ Si tiene alguna duda o requiere más información, con gusto la atenderemos y le suministraremos toda la información.
- ✓ Si finalmente, decide aceptar nuestra invitación a participar, amablemente le solicitamos, firmar el Consentimiento Informado que se encuentra al respaldo, para proceder a realizar las pruebas.

Para cualquier información, puede contactar a cualquiera de las siguientes personas:

Dra Diana Maria Muñoz Perez Bacteriologa celular 3116415585 email:
diana.2291424565@ucaldas.edu.co

Dra. Clara-Helena González-Correa, Médica, Nutrióloga y PhD, celular 313-6505244, teléfono oficina en la Universidad de Caldas: (6)-8781500, extensión 14160,. Email: clara.gonzalez@ucaldas.edu.co

Anexo 4. Consentimiento informado.

CONSENTIMIENTO INFORMADO - PROYECTO DE INVESTIGACIÓN: "Efecto de una dieta antiinflamatoria sobre la expresión génica postprandial en mononucleares de adultos con obesidad"

Por favor, marque **SI** ó **NO** según corresponda en cada pregunta:	**SI**	**NO**
1. Soy mayor de edad, es decir, tengo 18 años ó más.		
2. Diligencié la Encuesta previa, donde se verificaron los requisitos de inclusión en el proyecto también que no tenga problemas de salud u otras situaciones que impidan o limiten la realización de las pruebas o que impliquen un mayor riesgo del mínimo.		
3. Entendí la Hoja de Información. Se me explicó verbalmente y tuve la oportunidad de plantear inquietudes y dudas, que fueron respondidas satisfactoriamente.		
4. Mi participación es voluntaria. No se ha ejercido ningún tipo de presión y entiendo que me puedo retirar en cualquier momento del estudio, sin que ello tenga ninguna implicación negativa para mí. En caso de retirarme, estoy en libertad de dar o no explicaciones sobre los motivos.		
5. Entiendo que la información que se recolecte sobre mí es de carácter confidencial, que será manejada de manera anónima, y que únicamente podrá ser consultada por los investigadores del proyecto.		
6. Acepto que los resultados sean utilizados de manera anónima en publicaciones de carácter científico, que las muestras sean guardadas en un banco de muestras y puedan ser analizadas en el exterior.		
7. Acepto que las muestras y los resultados puedan ser utilizadas de forma anónima para investigaciones posteriores.		
8. Cuento con servicios de atención en salud (EPS) y/o Seguro de Accidentes.		
9. Me comprometo a seguir con todas las indicaciones de la dieta y asistir a las citas programadas de control y seguimiento con el fin de cumplirla en su totalidad.		
10. Acepto participar en el programa arriba mencionado.		
Estoy afiliada a la EPS:_____y a la Compañía de Seguros: _____ En caso de accidente o urgencia, puedo ser atendida en: _____		

_____ _____
Nombre de la voluntaria Firma de la voluntaria
Fecha Cédula #: _____

_____. _____
Nombre del testigo Firma del testigo
Cédula #: _____

Anexo 5. Historia clínica. Verificación de los criterios de inclusión

FORMATO 2. HISTORIA CLINICA

PROYECTO DE INVESTIGACION: **Efecto de una dieta antiinflamatoria sobre la expresión génica postprandial en mononucleares de adultos con obesidad.**

NOMBRE:_____ **FECHA:** Día___Mes____Año ___

La información solicitada a continuación es requerida para verificar: los criterios de inclusión en el proyecto, su estado general de salud y que podrá realizar las pruebas sin arriesgar su seguridad e integridad, por lo tanto, es su responsabilidad garantizar su veracidad. Todos sus datos serán manejados de manera confidencial y anónima.

CRITERIOS DE EXCLUSIÓN

Enfermedades diagnosticadas:

- ✓ DM: SI___ NO____
- ✓ Hipotiroidismo: SI____NO_____
- ✓ Enf. Inflamatorias: SI____NO_____
- ✓ Consume bebidas alcohólicas: SI____ NO____ con qué frecuencia:_____
- ✓ Consume cigarrillo o sustancias psicoactivas: SI____ NO_
- ✓ Se encuentra en Programas de reducción de peso: SI____ NO_ NO
- ✓ Se encuentra tomando algún medicamento: SI____ NO____ Cual_____
- ✓ Se encuentra embarazada o sospecha de estarlo: SI____

- ✓ Planifica SI_____NO

Enfermedades familiares: HTA: DM Dislipidemias Obesidad Hipotiroidismo

Fecha nacimiento (día/mes/año):	Edad cumplida en años:
Lugar de nacimiento:	Cédula de ciudadanía #:
Dirección	Estrato
Correo electrónico:	
Celular:	Teléfono Fijo:
Estatura aproximada (cm):	Peso aproximado (kg)
Fecha de último día de menstruación (día/mes):	Duración menstruación en días:

Método de planificación:	Ocupación y Empresa:
Grupo Étnico: ( ) Indígena ( ) Afrocolombiano ( ) Mestizo ( ) Blanco ( ) Otro. Cuál?	
Lugar de nacimiento PADRE:	MADRE:
Lugar de nacimiento ABUELO PATERNO:	ABUELO MATERNO:
Lugar de nacimiento ABUELA PATERNA:	ABUELA MATERNA:

1 y 2. VALORACION NUTRICIONAL Y DE LA CONDICION FÍSICA	**SI**	**NO**
1. ¿El médico le ha informado que tiene algún problema del corazón?		
2. ¿Le ha dolido el corazón o el pecho en algún momento?		
3. ¿Ha sufrido recientemente o sufre con frecuencia desmayos o mareos?		
4. ¿Tiene algún problema de huesos o articulaciones que le impida hacer ejercicio?		

Anexo 6. Anamnesis alimentaria o recordatorio de 24 horas.

PROYECTO DE INVESTIGACION : **Efecto de una dieta antiinflamatoria sobre la expresión génica postprandial en mononucleares de adultos con obesidad.**

SEGUIMIENTO Y CONTROL SEMANAL

NOMBRE:_____**FECHA:** Día_____Mes___Año _____

PESO**:**_____**Kg** CINTURA**: Menor**_____**Media**_____**Ombligo**___*TOTAL*_____CADERA**:**

PREPARACION (Nombre de las preparaciones, por ejemplo café con leche, arroz con leche, etc) **DESAYUNO**	**MEDIDA CASERA** Pocillo, taza, cuchara pequeña, cuchara sopera.	**INGREDIENTES** incluya azúcar, sal, margarina, mayonesa, salsas
MEDIA MAÑANA	**MEDIDA CASERA**	**INGREDIENTES**
ALMUERZO	**MEDIDA CASERA**	**INGREDIENTES**
ALGO	**MEDIDA CASERA**	**INGREDIENTES**
COMIDA	**MEDIDA CASERA**	**INGREDIENTES**
MERIENDA	**MEDIDA CASERA**	**INGREDIENTES**

Grupo De alimentos	**INGERIDOS**	**RECOMENDADOS**	**DEFICIT**	**EXCESO**
LECHES				
QUESOS				
CARNES				
LEGUMINOSAS				

HARINAS				
GRASAS				
FRUTAS				
VERDURAS				
AZUCARES				

OBSERVACIONES:_

_____

CONDUCTA_____

FIRMA INVESTIGADOR_____ **FIRMA PARTICIPANTE**_____

Anexo 7. Hoja de recolección de datos de la valoración nutricional.

Proyecto de investigación: **Efecto de una dieta antiinflamatoria sobre la expresión génica postprandial en mononucleares de adultos con obesidad.**

FECHA: (dd/mm/aa)				**Código**	**Promedio**
Nombre:					
Fecha de nacimiento:			**Años**		
Estatura cm		**1. Medición**	**2. Medición**	**3. Medición**	
Peso Kg (ayunas)					
Indice de masa corporal IMC Kg/m2					
Presion Arterial (Brazo derecho)					
Fuerza de agarre		**1. Medición**	**2. Medición**	**3. Medición**	
Dominancia: Diestro ( )			**Zurdo( )**		
Pliegues		**1. Medición**	**2. Medición**	**3. Medición**	
% Grasa pliegues					
Circunferencias		**1. Medición**	**2. Medición**	**3. Medición**	
Cintura media					
Cadera					
Índice CC					

Laboratorios:

Examinadores: Diana Muñoz Elcy Astudillo

Anexo 8. Guia alimentaria y recomendaciones generales para el seguimiento de la dieta.

RECOMENDACIONES GENERALES

1. Coma despacio y mastique bien, esto para efectos de una buena digestión
2. Utilice únicamente el número de porciones recomendadas
3. Establezca horarios regulares en su alimentación
4. Use solamente aceites de origen vegetal (preferible de canola girasol, soya)
5. Consuma carnes pulpas y el pollo sin piel
6. Manténgase una buena hidratación entre las comidas
7. Las porciones de grasa programada están incluidas en la preparación de los alimentos
8. Consuma la mayor parte de las frutas enteras y no tome más de un vaso de jugo al día
9. Consuma aromáticas, café, té verde, bebida de jengibre sin azúcar, entre las comidas
10. Si consume vino no pase de 1 copa (150ml x copa) al día
11. Si toma edulcorantes. Consuma máximo hasta 1 porciones al día
12. Se recomienda consumir maní o nueces una porción al día.
13. Prepare los alimentos con especias como: cilantro, tomillo, orégano, albahaca, ajonjolí, curry, ajo, cebolla y tomate.
14. Evite utilizar sazonadores artificiales (pastillas con sabores a carne o pollo).
15. Consuma pescado 3 veces por semana
16. Evite consumir carne roja más de 1 veces a la semana
17. Consuma máximo 3 huevos por semana
18. Consuma chocolate al menos 3 veces por semana
19. Consuma leguminosas (frijol, arveja, lenteja, garbanzo) 2 a 3 veces por semana y en estas ocasiones evite comer carne
20. consuma diariamente una porción de aguacate.
21. Evite consumir alimentos procesados (salchicha, chorizos, jamón…)
22. Evite consumir alimentos de paquete (papas, chicharrón, tacos…)

Las indicaciones de este plan alimentario fueron elaboradas de acuerdo con sus características individuales, por lo que ES DE USO EXCLUSIVO.

GUIA ALIMENTARIA

Fecha: Dia_____Mes_____Año_____

Nombre: _

V.C.T:_____Kcal_____ Kj_____Proteína:_____

Grasas: _____ Carbohidratos: _____ Otros:_____

DISTRIBUCION DE LAS COMIDAS DEL DIA

GRUPO DE ALIMENTOS	No. De intercambios	Desayuno	Media mañana	Almuerzo	Algo	Comida
Leches						
Queso sustituto						
Harinas						
Carnes leguminosas						
Grasas						
Frutas						
Verduras						
Azúcares						

Leche entera pasteurizada	1 vaso	Yogurt	1 vaso
Leche en polvo	5 cdas sop	Kumis	1 vaso
Leche baja en grasa pasteurizada	1 vaso		

QUESO SUSTITUTO: Cantidad:_____porciones diarias

Queso cuajada	1 tajada
Huevo de codorniz	5 unidades
Huevo de gallina	1 unidad

CARNES Cantidad:_____porciones diarias**.**

Carne <10% grasa res	100g	Callo o panza	100g
Carne de cerdo <10% grasa	100g	**Trucha**	100g
Pollo sin piel	1 muslo	Pescado	100g
Hígado	100g	**Atún**	½ lata
Lengua	100g	**sardina**	

LEGUMINOSAS. Cantidad: ____porciones diarias.

Fríjol toda variedad	4 c.das soperas
Lentejas	4 c.das soperas
Arveja seca	4 c.das soperas
Garbanzos	4 c.das soperas
Soya	4 cucharadas
Soya semillas	1 paquete de 30 g

HARINAS: Cantidad:_____porciones diarias

Arroz cocido integral	4 cdas	Maíz cocido	½ pocillo
Avena en hojuelas	4 cdas	Papa cocida	1 mediana
Arepa delgada integral	1 und. (Med)	Arracacha	1 und (med)
Espaguetis integral	½ pocillo	Papa criolla pequeñas	3 und.
Pan integral	1 tajada	Yuca blanca	1 trozo
Pan mogolla integral	1 und	Guineo verde	1 und
Galletas integrales	3 tablas	Plátano verde/ maduro	½ und
Pan francés (especias)	1 trozo	Tajadas de plátano	3 unds.
Tostadas integrales	1 und	Colada de maizena	2 cdas

GRASAS: Cantidad:_____porciones diarias

Aceite de soya	1 c.dita	**Maní**	10 granos
Aceite de maíz	1 c.dita	**Nueces**	4 unidades
Aceite de girasol	1 c.dita	**Aguacate**	¼ und
Aceite de canola	1 c.dita	Margarina	1 c.dita
Linasa	1 cucharada	**Almendras**	5 unidades

AZUCARES Cantidad:_____porciones diarias

Panela	**1 trozo**	Bocadillo de guayaba	1 und
Azúcar morena	2 cdas	Chocolatina dietética	2 und
Miel	1 c.da sop	Helado dietético	1 und
Chocolate negro (1pastilla)	1 pocillo(240ml)	Gelatina de pata	1 unidad
Agua de panela (trozo)	1 pocillo(240ml)		

FRUTAS. Cantidad: _____ porciones diarias

Granadilla	**3 und.**	Zapote	1 und.
Uchuvas	**10 -12 unidades**		
Guayaba rosada	**2 und. Med**		
Mandarina	**1 unidad**		
Manzana	**1 und. Peq**		
Chontaduro	**2 medianos**		
Uva negra	10-12 unidades	**JUGOS**	**1 vaso**
Papaya	1 trozo	Mora	
Mango	1 und. peq	Curuba	
Fresa	12-15 und.	Tomate de árbol	
Piña	1 tajada	Maracuyá	
Naranja	1 vaso	Mora castilla	
Sandia	1 trozo	uva	
Anón	½ und. Peq		
Melón redondo	1 trozo		
Parpayuela	1 und. Peq	Banano bocadillo	2 unds
Banano común	½ unidad		

VERDURAS: Cantidad:____porciones diarias

Cebolla cabezona	½ pocillo	Lechuga común	2 poc.
Pepino cohombro	1 poc.	Brócoli crudo	1 poc.
Rábano rojo	1 poc.	Habichuela	1 poc.
Apio tallo crudo	2/3 poc.	**Zanahoria cruda**	**1 poc.**
Remolacha cruda	2/3 poc.	**Tomate rojo crudo**	**1 und. peq**
Repollo crudo	1 ½ poc.	**Espinaca**	**1 pocillo**
Cilantro	¼ pocillo	Auyama	1 trozo
Cidra	1 pocillo	Pimentón	1 pocillo

Anexo 9. Certificado de la participación en el programa Análisis por Transcriptómica.

UNIVERSIDAD EAFIT

CENTRO DE EDUCACIÓN CONTINUA

C E C

CERTIFICA QUE

DIANA MARÍA MUÑOZ

C.C. 42071578

Asistió al Programa

ANÁLISIS POR TRANSCRIPTÓMICA

Programa de extensión

20 horas de actividades académicas

Medellín, Colombia, 06 de marzo de 2015

Luis Fernando Rendón Cortés

Director de Educación Continua

UNIVERSIDAD EAFIT

Sergio Augusto Ramírez Echeverri

Coordinador Académico del Programa

UNIVERSIDAD EAFIT

Anexo 10. Certificado Programa de Capacitación en Escritura Académica y Presentaciones orales en Contextos Académicos.

MAESTRÍA EN DIDÁCTICA DEL INGLÉS

Calle 65 No. 26-10 PBX: 8781500 - Telefax: 8781501
E-mail: vcinlder@ucaldas.edu.co - www.ucaldas.edu.co
Apartado Aéreo: 275 Manizales - Colombia

UNIVERSIDAD DE CALDAS
MAESTRÍA EN DIDÁCTICA DEL INGLÉS

Hacen constar que

DIANA MARÍA MUÑOZ PEREZ

Participó dentro del Marco del Convenio Específico de Cooperación Celebrado entre la Vicerrectoría de Investigaciones y Postgrados de la Universidad de Caldas y el Centro de Bioinformática y Biología de Colombia Computacional de Colombia (BIOS) en el:

"Programa de Capacitación en Escritura Académica y Presentaciones Orales en Contextos Académicos"

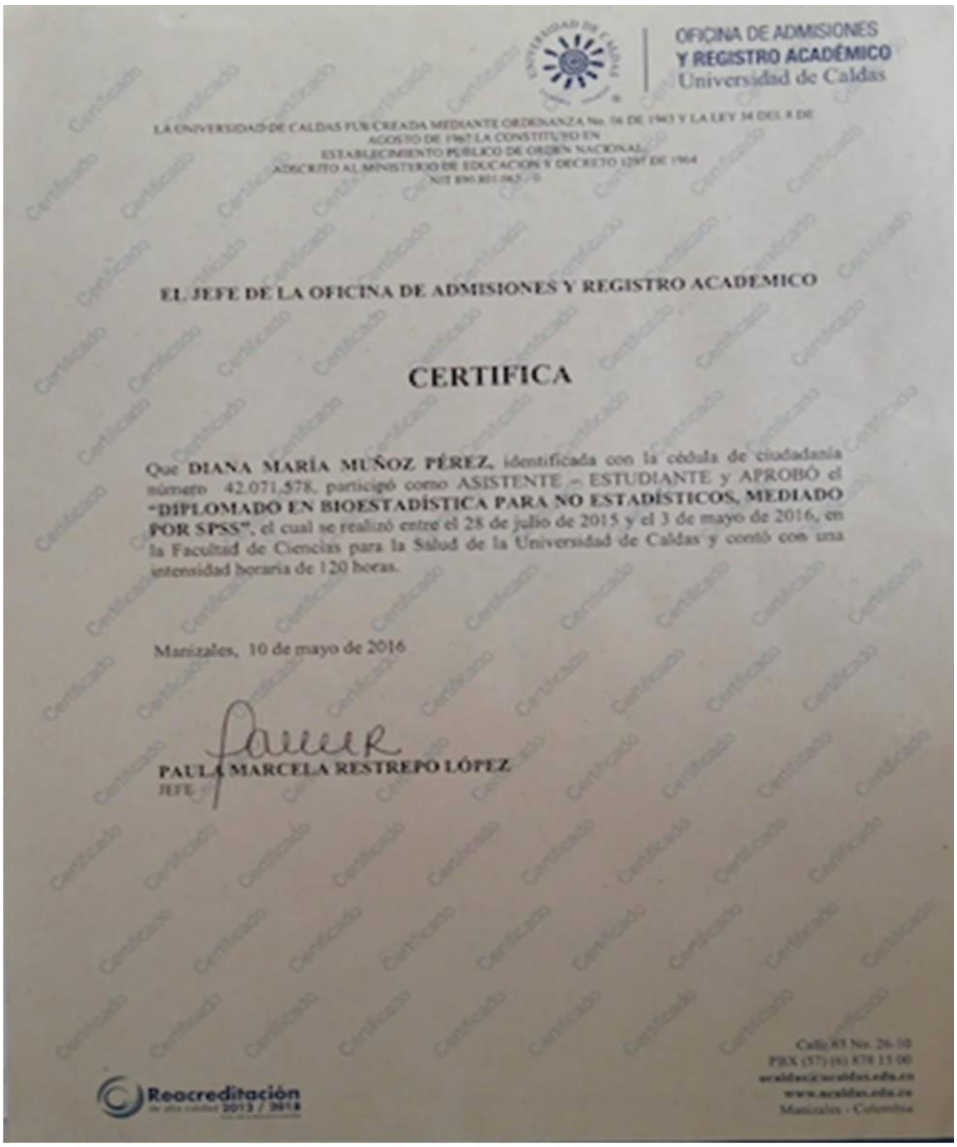
Total Horas: 60

Para constancia se firma en Manizales, a los 10 días del mes de Diciembre de 2015.

Margarita María López Pinzón
Coordinadora Maestría en Didáctica del Inglés

Acreditación Institucional de Alta Calidad: Antes un compromiso, hoy un reto permanente

Anexo 11. Certificado “Diplomado en Bioestadística para no Estadisticos, Mediado por SPSS"



OFICINA DE ADMISIONES
Y REGISTRO ACADÉMICO
Universidad de Caldas

LA UNIVERSIDAD DE CALDAS FUE CREADA MEDIANTE ORDENANZA No. 06 DE 1943 Y LA LEY 34 DEL 8 DE AGOSTO DE 1967 LA CONSTITUYO EN ESTABLECIMIENTO PUBLICO DE ORDEN NACIONAL ADSCRITO AL MINISTERIO DE EDUCACION Y DECRETO 1297 DE 1964
NIT 890.801.063 - 0

EL JEFE DE LA OFICINA DE ADMISIONES Y REGISTRO ACADEMICO

CERTIFICA

Que **DIANA MARÍA MUÑOZ PÉREZ**, identificada con la cédula de ciudadanía número 42.071.578, participó como ASISTENTE – ESTUDIANTE y APROBÓ el **"DIPLOMADO EN BIOESTADÍSTICA PARA NO ESTADÍSTICOS, MEDIADO POR SPSS"**, el cual se realizó entre el 28 de julio de 2015 y el 3 de mayo de 2016, en la Facultad de Ciencias para la Salud de la Universidad de Caldas y contó con una intensidad horaria de 120 horas.

Manizales, 10 de mayo de 2016

PAULA MARCELA RESTREPO LÓPEZ
JEFE

Reacreditación de alta calidad 2013 / 2018

Calle 65 No. 26-10
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www.ucaldas.edu.co
Manizales - Colombia

Anexo 12. Aceptación Pasantía Nacional en el Instituto Técnico Metropolitano de Medellín.

Institución Universitaria
Acreditada en Alta Calidad

Medellín, 2 de noviembre de 2016

Estudiante
DIANA MARIA MUÑOZ PEREZA
Universidad de Caldas

Cordial saludo Diana:

En primer lugar, quiero agradecer su interés en el Instituto Tecnológico Metropolitano para realizar su estancia de investigación por una duración de 10 días, en el Laboratorio de Investigación en Ciencias Biomédicas, para la estandarización de métodos de extracción de ARN y Proteínas a partir de células de sangra periférica, debido a la experiencia de nuestro Grupo de Investigación e Innovación Biomédica GI2B, en el área de la Biología Molecular.

Una vez surtido todo el proceso interno para la valoración de la pertinencia de tu solicitud, paso a informarle que ésta ha sido aceptada con todos los avales y documentación anexa.

Para efectos de la legalización definitiva, le agradezco enviarnos una carta donde consten las fechas definitivas de realización de su pasantía en nuestra institución.

Cordialmente,

MARIA FERNANDA VEGA DE MENDOZA
Directora Cooperación y RRII

Anexo 13. Certificado Pasantía Internacional corta. Universidad de Guadalajara. México.

Universidad de Guadalajara
Centro Universitario de Ciencias de la Salud
Departamento de Biologia Molecular y Genomica
Laboratorio de Biologia Molecular en Medicina
Hospital Civil "Fray Antonio Alcalde"

DRA. CLARA HELENA GONZÁLEZ CORREA
PRESENTE.

Por medio de la presente me permito enviarle un cordial saludo y a la vez quiero externarle la oportunidad que me dio de interaccionar con sus estudiantes de Doctorado.

Al mismo tiempo quiero realizarle un reporte de la evaluación de la Presentación de la propuesta de proyecto de tesis titulado: **Efecto de una dieta anti inflamatoria sobre la expresión génica postprandial de células mononucleares de mujeres adultas con sobrepeso u obesidad**, presentado por la alumna **Diana María Muñoz Pérez**.

La bacterióloga Diana Muñoz presentó su trabajo en donde menciona la prevalencia de sobrepeso y obesidad, a nivel mundial y en Colombia; y mostró la relación existente entre estas patologías y las principales comorbilidades asociadas al exceso de peso. Posteriormente, explicó de manera detallada el papel que tiene el tejido adiposo y la ganancia del mismo en activar la vía de NF-kB. Entre los genes que responden a la activación de NF-kB se encuentran genes del estrés oxidativo (*ADAM, AKT1, SOD2*), inflamación (*IL-2, IL-6, IL-8, rIL2, IL-12, IL-1B, MCP1, TNF alfa, NFKB1A*), función endotelial (*VCAM, ICAM*) y apoptosis (*MMP-9, IFNB1, IFN gamma*). Además, en la sección de los antecedentes presentó información que demuestra el efecto que tienen los nutrimentos en activar diferentes niveles de regulación a nivel celular. Y se presentaron algunos antecedentes directos del papel de la alimentación en la regulación de genes

Anexo 14. Certificado Pasantía Internacional. Instituto Maimónides de Investigación Biomédica de Córdoba España.

IMIBIC INSTITUTO MAIMÓNIDES DE INVESTIGACIÓN BIOMÉDICA DE CÓRDOBA

Córdoba, Diciembre 7 de 2018

Doctora
Clara Helena González Correa.
Facultad de Ciencias Exactas y Naturales
Doctorado en Ciencias Biomédicas
Universidad de Caldas

Cordial Saludo,

Por medio de la presente certificamos que la estudiante de doctorado en ciencias biomédicas de la Universidad de Caldas Diana María Muñoz Pérez, durante el segundo semestre del año 2018 realizó experimentos relacionados con expresión génica, microbiota intestinal, western blot y metilación del ADN en el marco del proyecto "Efecto de una dieta antiinflamatoria sobre la expresión génica postprandial en mononucleares de adultos con obesidad" en el Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC) con el grupo GC 09: Nutrigenomica y Síndrome metabólico.

Los profesores Oriol Rangel Zúñiga PhD y Antonio Camargo. PhD evaluamos el desempeño de la estudiante durante el semestre y decidimos asignar una nota de 5.0 (cinco)

Atentamente,

Oriol Rangel Zúñiga PhD
Investigador Postdoctoral
IMIBIC

Antonio Camargo PhD
Investigador Postdoctoral
IMIBIC

IMIBIC INSTITUTO MAIMÓNIDES DE INVESTIGACIÓN BIOMÉDICA DE CÓRDOBA

Dentro del Marco de Entendimiento firmado entre la Fundación para la Investigación Biomédica de Córdoba (FIBICO-IMIBIC) y la Universidad de Caldas, los Drs. Antonio Camargo García identificado con DNI 30943261G, y Oriol Alberto Rangel Zuñiga identificado con NIE X4842611F

CERTIFICAN

Que la estudiante de doctorado en ciencias biomédicas de la Universidad de Caldas, Diana Muñoz Pérez, identificada con pasaporte nº AR614159, llevó a cabo su estancia pre doctoral entre el 2 de Julio y el 7 de diciembre de 2018. Durante este período la estudiante llevó a cabo los ensayos de laboratorio orientados a lograr el objetivo del proyecto " Efecto de una dieta antiinflamatoria sobre la expresión génica postprandial en mononucleares de adultos obesos ". El presente trabajo estuvo bajo nuestra tutela y se llevo a cabo con amplia eficiencia y aprovechamiento.

En constancia firman en Córdoba a 7 de Diciembre de 2018.

Dr. Antonio Camargo García
Investigador Postdoctoral

Dr. Oriol Alberto Rangel Zuñiga
Investigador Postdoctoral

Anexo 15. Certificado participación en evento científico.

XVI CONGRESO COLOMBIANO Y X CONGRESO INTERNACIONAL DE GENÉTICA HUMANA
Eje Cafetero

CERTIFICADO PONENCIA

La Asociación Colombiana de Genética Humana, Comfamiliar Risaralda y su Fundación Universitaria Comfamiliar certifican presentación de Trabajo Libre otorgado a:

DIANA MARÍA MUÑOZ PÉREZ

Efecto De Una Dieta Suplementada Con Frutas, Aguacate, Granos Enteros Y Trucha Sobre La Expresión Génica Postprandial En Adultos Con Obesidad.

En la modalidad Presentación en Ponencia

Presentado en el **XVI Congreso Colombiano y X Congreso Internacional de Genética Humana**, realizado entre el 14 y 16 de octubre de 2021.

Dra. Carolina Rivera	*Dra. Gloria Liliana Porras Hurtado*	*Oscar Javier Zapata Gómez*
Presidente de la Asociación Colombiana de Genética Humana	*Presidente del Congreso ACGH-Comfamiliar*	*Rector Fundación Universitaria Comfamiliar*

Se expide en la ciudad de Pereira, Risaralda, Colombia a los 16 días del mes de octubre del año 2021.

ORGANIZA

ACGH Asociación Colombiana de Genética Humana · FUNDACIÓN UNIVERSITARIA COMFAMILIAR RISARALDA · Comfamiliar RISARALDA