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ANA GABRIELLA PEREIRA ALVES

Níveis séricos e efeito da suplementação de vitamina D sobre a composição corporal e perfil metabólico de crianças

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ANA GABRIELLA PEREIRA ALVES

Níveis séricos e efeito da suplementação de vitamina D sobre a composição corporal e perfil metabólico de crianças

Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Goiás para obtenção do Título de Doutora em Ciências da Saúde.

Orientadora: Profª Dra. Maria Sebastiana Silva

Goiânia
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Ata nº **39/2020** da sessão de Defesa de Tese de **Ana Gabriella Pereira Alves**, que confere o título de Doutora em **Ciências da Saúde**, na área de concentração em **DINÂMICA DO PROCESSO SAÚDE-DOENÇA.**

Aos **vinte e um de dezembro de dois mil e vinte**, a partir das **08:00h**, **por meio de videoconferência**, realizou-se a sessão pública de Defesa de Tese intitulada **"Níveis séricos e efeito da suplementação de vitamina D sobre a composição corporal e perfil metabólico de crianças"**. Os trabalhos foram instalados pela Orientadora, Professora Doutora **Maria Sebastiana Silva (FEFD/UFG)** com a participação dos demais membros da Banca Examinadora: Professora Doutora **Karine Anusca Martins (FANUT/UFG)**, membro titular externo; Professora Doutora **Renata Carvalho dos Santos (ESEFEGO/UEG)**, membro titular externo, Professora Doutora **Maria Claret Costa Monteiro Hadler (FANUT/UFG),** membro titular interno; Professora Doutora **Lídia Andreu Guillo (ICB/UFG)**, membro titular interno. Durante a arguição os membros da banca **não fizeram** sugestão de alteração do título do trabalho. A Banca Examinadora reuniu-se em sessão secreta a fim de concluir o julgamento da Tese, tendo sido a candidata **aprovada** pelos seus membros. Proclamados os resultados pela Professora Doutora **Maria Sebastiana Silva**, Presidente da Banca Examinadora, foram encerrados os trabalhos e, para constar, lavrou-se a presente ata que é assinada pelos Membros da Banca Examinadora, aos **vinte e um de dezembro de dois mil e vinte**.

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Data: 21/12/2020

Dedico este trabalho à minha querida mãe!

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SUMÁRIO

TABELAS, FIGURAS E QUADROS

SÍMBOLOS, SIGLAS E ABREVIATURAS

%GC:	Percentual de Gordura Corporal
%VD:	Percentual de Valor Diário
α:	Alfa
β:	Beta
γ:	Gama
$1,25(OH)_2D$:	1,25-Dihidroxivitamina D
24-OHase:	25-Hidroxivitamina D_3-24-Hidroxilase
25(OH)D:	25-Hidroxivitamina D
7-DHC:	7-Deidrocolesterol
AAP:	American Academy of Pediatrics
ABCA1:	ATP-Binding Membrane Cassette Transporter A1 (Proteína A1 de Ligação ao ATP)
AI:	Ingestão adequada
CAAE:	Certificado de Apresentação para Apreciação Ética
CC:	Circunferência da Cintura
CLAE-DAD:	Cromatografia líquida de alta eficiência com detector de arranjo de diodos
CT:	Colesterol Total
DBP:	Vitamin D Binding Protein (Proteína Ligante da Vitamina D)
DCT:	Dobra Cutânea Tricipital
DCSE:	Dobra Cutânea Subescapular
DCV:	Doenças Cardiovasculares
DM2:	Diabetes *Mellitus* tipo 2
FPS:	Fator de Proteção Solar
FTO:	Fat Mass and Obesity-Associated Gene (Gene Associado à Obesidade)
GJ:	Glicemia de Jejum
GP:	Grupo Placebo
GS:	Grupo Suplementado
HAS:	Hipertensão Arterial Sistêmica
HDL-c:	High-Density Lipoprotein Cholesterol (Lipoproteína de Alta Densidade)
HMGR:	3-Hydroxy-3-Methylglutaryl-CoA Reductase (3-Hidroxi-3-Metilglutaril Coenzima A Redutase)
HPLC:	High-Performance Liquid Chromatography (Cromatografia Líquida de Alta Resolução)
IMC:	Índice de Massa Corporal
IOM:	Institute of Medicine

ISAK: International Society for the Advancement of Kinanthropometry
LDL-c: Low-Density Lipoprotein Cholesterol (Lipoproteína de Baixa Densidade)
MLG: Massa Livre de Gordura
PAD: Pressão Arterial Diastólica
PAQ-C: Physical Activity Questionnaire for Older Children (Questionário de Atividade Física Regular)
PAS: Pressão Arterial Sistólica
PPARγ: Peroxisome Proliferator-Activated Receptors γ (Receptor Ativador de Proliferação de Peroxissomos γ)
PTH: Paratormônio
RCE: Relação Cintura-Estatura
RDA: Recommended Dietary Allowances (Ingestão Diária Recomendada)
ReBEC: Registro Brasileiro de Ensaios Clínicos
RIA: Radioimunoensaio
RPM: Rotações por Minuto
TALE: Termos de Assentimento Livre e Esclarecido
TCLE: Termos de Consentimento Livre e Esclarecido
TG: Triglicerídeos
UBS: Unidade Básica de Saúde
UFG: Universidade Federal de Goiás
UI: Unidades Internacionais
UL: Upper Level Intake (Ingestão Máxima Tolerada)
UTN: Universal Trial Number (Número Universal de Ensaios)
UVB: Ultravioleta B
VDR: Vitamin D Receptor (Receptor de Vitamina D)
VSMC: Vascular Smooth Muscle Cell (Células Musculares Lisas Vasculares)

RESUMO

Introdução: A vitamina D participa de diversas vias metabólicas do organismo, incluindo a diferenciação e proliferação celular, controle hormonal, modulação da inflamação e regulação do sistema imune. Visto que receptores de vitamina D estão presentes em diferentes tecidos e órgãos, ela apresenta relação com diversas doenças, como a obesidade, hipertensão arterial sistêmica e dislipidemia. **Objetivo:** Avaliar os níveis séricos e o efeito da suplementação de vitamina D sobre a composição corporal e perfil metabólico de crianças. **Métodos:** Realizou-se um ensaio clínico randomizado, placebo-controlado, triplo-cego, cruzado (*crossover*) com 62 crianças de quatro a 11 anos de idade, de uma instituição pública de ensino, que atenderam aos critérios de seleção. Foram coletados dados sociodemográficos, econômicos e uso de protetor solar a partir de um questionário específico; a área corporal diariamente exposta ao sol foi avaliada por meio de um questionário com uma figura representativa do percentual corporal; foi utilizado um questionário específico para a avaliação da atividade física e comportamento sedentário; a antropometria (massa corporal e estatura) e composição corporal (circunferência da cintura, percentual de gordura corporal, massa livre de gordura e dobras cutâneas tricipital e subescapular) foram obtidas com a utilização de estadiômetro, balança eletrônica, fita antropométrica, bioimpedância tetrapolar e adipômetro; a pressão arterial foi aferida com monitor digital automático; as concentrações de 25-hidroxivitamina D [25(OH)D], glicose de jejum e frações lipídicas foram analisadas no sangue; e o consumo alimentar avaliado por meio do recordatório de 24 horas. No estudo de intervenção, os grupos suplementado e placebo receberam cinco gotas de colecalciferol (equivalente a 1000 UI/dia) e cinco gotas de óleo de girassol, respectivamente, por 12 semanas, separados por um período de *washout* de 10 semanas. **Resultados:** Entre as crianças com níveis séricos de vitamina D suficiente (≥ 75 nmol/L) (n=88), que participaram do estudo de linha de base, não foi encontrada diferença no sexo, raça auto-referida, prática de atividade física, idade, antropometria, composição corporal, parâmetros bioquímicos e pressão arterial entre as crianças com 25(OH)D 75-99 e ≥ 100

nmol/L, além da não associação da 25(OH)D com a composição corporal e o perfil metabólico. No estudo *crossover*, realizado com crianças hipertrigliceridêmicas, a suplementação com colecalciferol reduziu as concentrações séricas de colesterol total (CT) ($p < 0,001$), LDL-c ($p < 0,001$), não HDL-c ($p < 0,001$) e das frações CT/HDL-c ($p = 0,001$) e LDL-c/HDL-c ($p < 0,001$), quando comparado ao grupo placebo. **Conclusões:** A vitamina D sérica não se associou com a composição corporal e o perfil metabólico de crianças com 25(OH)D ≥ 75 nmol/L, e a suplementação de 1000 UI/dia de colecalciferol, por 90 dias, em crianças hipertrigliceridêmicas e sem deficiência sérica de 25(OH)D, foi capaz de melhorar o perfil lipídico.

Palavras-chave: Colecalciferol, lipoproteína, composição corporal, criança.

ABSTRACT

Introduction: Vitamin D plays a role in several metabolic pathways, including cell diferentiation and proliferation, hormonal control, modulation of inflammation and immune system regulation. Since vitamin D receptors are presented in different tissues and organs, it is related to many diseases, such as obesity, hipertension and dyslipidemia. **Objective:** To evaluate the serum levels and the effect of cholecalciferol supplementation on body composition and metabolic profile in of children. **Methods:** A randomized, placebo-controlled, triple-blind, crossover study was conducted with 62 children, 4 to 11 years old, from a public educational institution, that met the selection criteria. Sociodemographic, economic and sunscreen use data were collected from a specific questionnaire; the body area daily exposed to the sun was evaluated by a questionnaire with a representative figure of the body percentage; a specific questionnaire was used to evaluate physical activity and sedentary behavior; anthropometry (body mass and height) and body composition (waist circumference, body fat percentage, fat-free mass, triceps and subscapular skinfolds) were obtained using a stadiometer, electronic scale, anthropometric tape, tetrapolar bioimpedance and adipometer; blood pressure was measured using an automatic digital monitor; 25-hydroxyvitamin D [25(OH)D], fasting glucose and lipid profile were analysed from blood collection; and food intake data was evaluated through the 24-hour recall. In the intervention study, the two groups, supplemented and placebo, received 5 drops of cholecalciferol (1000 IU/day) and 5 drops of sunflower oil (placebo), respectively, for 12 weeks, separated by 10-week washout period. **Results:** Among children with sufficient serum vitamin D (≥ 75 nmol/L), who participated in the baseline study, no difference was found in sex, self-reported race, physical activity, age, anthropometry, body composition, biochemical parameters and blood pressure between children with 25(OH)D 75-99 and ≥ 100 nmol/L, in addition to the non-association of 25(OH)D with body composition and metabolic profile. In the crossover study, conducted with hypertriglyceridemic children, cholecalciferol supplementation reduced serum total cholesterol (TC) ($p < 0.001$), LDL-c ($p < 0.001$), non HDL-c ($p < 0.001$),

TC/HDL-c ($p = 0.001$) and LDL-c/HDL-c ($p < 0.001$) ratio, when compared to placebo group. **Conclusions:** Serum vitamin D was not associated with body composition and metabolic profile among children with 25(OH) ≥ 75 nmol/L, and 1000 IU/day of cholecalciferol supplementation, for 90 days, in hypertriglyceridemic children without 25(OH)D serum deficiency, was able to improve lipid profile.

Keywords: Cholecalciferol, lipoprotein, body composition, children.

1 INTRODUÇÃO

A infância é marcada por modificações no sistema motor, cognitivo, social e emocional (BLACK et al., 2017). Neste sentido, a alimentação saudável tem papel fundamental no crescimento e desenvolvimento adequados das crianças, além de contribuir para uma melhor qualidade de vida quando adulto (YAKOOB; LO, 2017).

Contudo, com os eventos de transição nutricional das últimas décadas (MEHIO SIBAI et al., 2010), a alimentação na idade pediátrica passou a ter importância também na prevenção de doenças, sobretudo as cardiovasculares (DCV), e para tanto são priorizadas a redução no consumo de gorduras trans, saturadas, açúcar refinado e sódio e estimulados o consumo de cereais integrais, frutas e hortaliças para um aporte adequado de vitaminas e minerais (ELENBERG; SHAOUL, 2014).

Em relação a esses nutrientes, tem-se como exemplo a vitamina D, cuja deficiência está associada ao desenvolvimento de doenças como a hipertensão arterial sistêmica (HAS) (THOMAS et al., 2012), DCV, diabetes *mellitus* tipo 2 (DM2) (WANG, 2013), obesidade (SEO et al., 2013) e dislipidemia (WANG et al., 2016), sendo o último de interesse do presente estudo.

A hipertrigliceridemia é uma das classificações laboratoriais da dislipidemia (FALUDI et al., 2017), e sua prevalência na infância relaciona-se principalmente ao excesso de gordura corporal e a alimentação inadequada (VALAIYAPATHI; SUNIL; ASHRAF, 2017).

Além da sua participação na saúde dos ossos e dentes, a vitamina D participa da diferenciação e proliferação celular, controle hormonal, modulação da inflamação e regulação do sistema imune (INSTITUTE OF MEDICINE, 2011; HEANEY et al., 2008; JAMES, 2008; BSCHEIDER; BUTCHER, 2016; REYNOLDS; BRUCE, 2017). Ela pode ser adquirida por meio da exposição solar, consumo de alimentos ou suplementos (HOLICK, 2006), porém a maior parte da sua produção é endógena, a partir da

exposição da pele a radiação ultravioleta B (UVB), e menos de 10% das suas necessidades diárias são obtidas pela alimentação (HOLICK et al., 2011).

Considerando as orientações de controle à exposição solar, em detrimento do risco de desenvolvimento de câncer de pele, e a sua concentração baixa nos alimentos, a deficiência de vitamina D passa a ser uma preocupação (HOEL et al., 2016), fato que tem levado ao aumento da sua suplementação (HOLICK et al., 2011).

Diante desses achados, a manutenção dos níveis séricos de vitamina D dentro dos valores adequados demonstra fator importante para a saúde. Apesar da recomendação de que sua concentração sérica esteja ≥ 75 nmol/L em todas as faixas etárias, para assegurar as demandas fisiológicas sugere-se que ela se mantenha entre 100-150 nmol/L (HOLICK et al., 2011).

Existem evidências da importância da vitamina D na saúde infantil (HOLICK, 2007; MISRA et al., 2008), contudo necessitam-se de mais investigações para confirmação dos achados. Assim, para contribuir no entendimento da relação do status sérico da vitamina D com fatores de risco para DCV em crianças, hipotetizou-se que a suplementação de 1000 Unidades Internacionais (UI) de vitamina D, por 12 semanas, promove melhorias na composição corporal e perfil metabólico de crianças hipertrigliceridêmicas de quatro a 11 anos de idade.

Destaca-se ainda que os resultados do presente estudo podem confirmar os benefícios da suplementação de vitamina D entre crianças e assim contribuir com a redução de gasto público e privado no tratamento de doenças futuras (CAMPBELL et al., 2014).

2 REVISÃO BIBLIOGRÁFICA

2.1 HISTÓRICO DA VITAMINA D

A vitamina D é um metabólito lipossolúvel, considerado um pró-hormônio (TSIARAS; WEINSTOCK, 2011), importante para a regulação de diversas vias metabólicas no organismo (INSTITUTE OF MEDICINE, 2011).

Em 1919, ao observar que cachorros com raquitismo, ao receberem óleo de fígado de bacalhau, apresentaram reversão da doença, pensou-se primeiramente que esse efeito seria atribuído à vitamina A (MELLANBY, 1919). Porém, três anos depois, McCollum et al. (1922) ao extrair esse nutriente verificaram que o óleo de fígado de bacalhau continuava com a capacidade de curar o raquitismo, descobrindo então uma nova substância, que descreveram como vitamina D.

Em relação à produção endógena de vitamina D a partir da exposição solar, Huldschinsky (1919) e Chick, Palzell e Hume (1923) identificaram que crianças com raquitismo poderiam ser curadas ao se exporem ou ao sol ou à radiação ultravioleta artificial. E, posteriormente, Steenbock e Black (1925) identificaram que uma substância lipídica inativa presente na pele poderia ser ativada a partir da ação dos raios solares ultravioleta, sendo esta a maior forma de obtenção da vitamina D (HOLICK et al., 2011).

2.2 FORMAS MOLECULARES, ABSORÇÃO E ARMAZENAMENTO

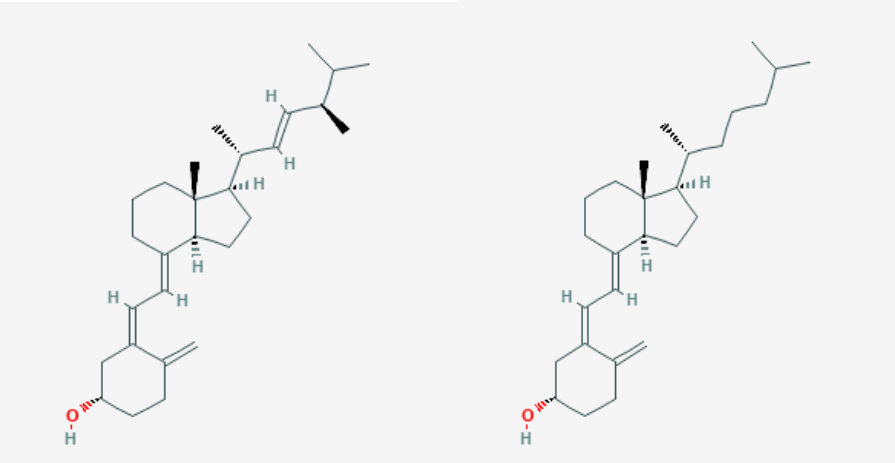
Há três formas de se obter a vitamina D, via alimentação (apesar de estar presente em uma pequena quantidade de alimentos), exposição solar ou uso de suplemento (INSTITUTE OF MEDICINE, 2011). Na alimentação, ela pode ser obtida nas formas de ergocalciferol (D_2) ou colecalciferol (D_3), ambas inativas, sendo a primeira de origem vegetal e a segunda animal (AMERICAN ACADEMY OF PEDIATRICS, 2014).

A vitamina D_2 ($C_{28}H_{44}O$) apresenta uma dupla ligação entre os carbonos 22 e 23 e um grupo metil no carbono 24, e a vitamina D_3 ($C_{27}H_{44}O$)

apresenta uma ligação simples entre os carbonos 22 e 23 e não possui o grupo metil no carbono 24 (Figura 1) (NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION, 2019a; 2019b).

A vitamina D é absorvida no intestino delgado, preferencialmente na presença de componente lipídico, por difusão passiva, sendo armazenada no fígado, tecido adiposo e muscular (HOLICK, 2003; ABBOUD et al., 2013; DAWSON-HUGHES et al., 2015). Contudo, a sua quantidade sérica, proveniente tanto da ingestão oral quanto da exposição solar, não equivale aos níveis armazenados no organismo (HOLICK, 2011).

Figura 1. Estrutura química das vitaminas D_2 e D_3.



Vitamina D_2 (Ergocalciferol) Vitamina D_3 (Colecalciferol)

Fonte: National Center for Biotechnology Information, 2019a; 2019b.

2.3 EXPOSIÇÃO SOLAR E CONVERSÃO DA FORMA ATIVA

Alguns fatores como poluição do ar, idade [com o passar do tempo há uma redução da quantidade de 7-deidrocolesterol (7-DHC) na pele], maior conteúdo de melanina na pele (quanto maior a pigmentação maior a barreira para a radiação ultravioleta B), e uso de protetor solar afetam a exposição da pele a irradiação dos raios ultravioleta B (AGARWAL et al. 2002; MACLAUGHLIN; HOLICK, 1985; MATSUOKA et al., 1995; MATSUOKA et al.,

1987), o que prejudica a síntese endógena de vitamina D. Ainda, antes das 10 e após as 15 horas as chances de ocorrer a síntese de vitamina D_3 é menor, devido ao ângulo de incidência dos raios solares estar mais oblíquo. Porém, é importante salientar que a exposição solar periódica entre esses horários aumenta o risco de câncer de pele, sendo assim, o incentivo à essa exposição deve ser feito com cautela (WACKER; HOLICK, 2013; HOEL et al., 2016).

A recomendação do tempo que o indivíduo deve permanecer exposto ao sol para se obter níveis adequados de vitamina D é variada, uma vez que esse processo é influenciado por diversos fatores, como a cor da pele, percentual da área corporal exposta ao sol e comprimento de onda dos raios ultravioleta (GILCHREST, 2008). Além disso, sabe-se que indivíduos com maior quantidade de melanina na pele necessitam, em média, de 5-10 vezes mais tempo expostos ao sol para a produção da mesma quantidade de vitamina D_3, quando comparado a uma pessoa com pouca melanina (MATSUOKA et al., 1995). De modo geral, de cinco a 30 minutos de exposição do rosto, braços, pernas ou costas sem protetor solar, no horário de 10 às 15 horas, duas vezes na semana, é suficiente para uma produção endógena adequada de vitamina D_3 (WACKER; HOLICK, 2013). A Sociedade Brasileira de Pediatria orienta, três vezes por semana, a exposição solar de 6-8 minutos, para crianças somente com fraldas, ou 17 minutos para aquelas com apenas as mãos e face expostas ao sol (SOCIEDADE BRASILEIRA DE PEDIATRIA, 2014).

Apenas a vitamina D_3 pode ser produzida endogenamente por meio da exposição solar (HOLICK, 2011). A radiação ultravioleta B, de comprimento de onda 290-320 nanômetros, incide na pele e converte o 7-DHC cutâneo (sintetizado no fígado a partir do colesterol), por meio de uma reação fotoquímica, em pré-vitamina D_3, que é convertida em vitamina D_3 (INSTITUTE OF MEDICINE, 2011; HOLICK, 2011).

Após a ingestão alimentar de vitamina D_2 ou vitamina D_3, ou produção deste último na pele, a vitamina D circula no organismo ligada à proteína ligante da vitamina D (DBP), e é transportada para o fígado. Neste órgão ocorre a primeira etapa de ativação da vitamina D que é a sua hidroxilação pela ação da enzima 25-hidroxilase, formando a 25-hidroxivitamina D

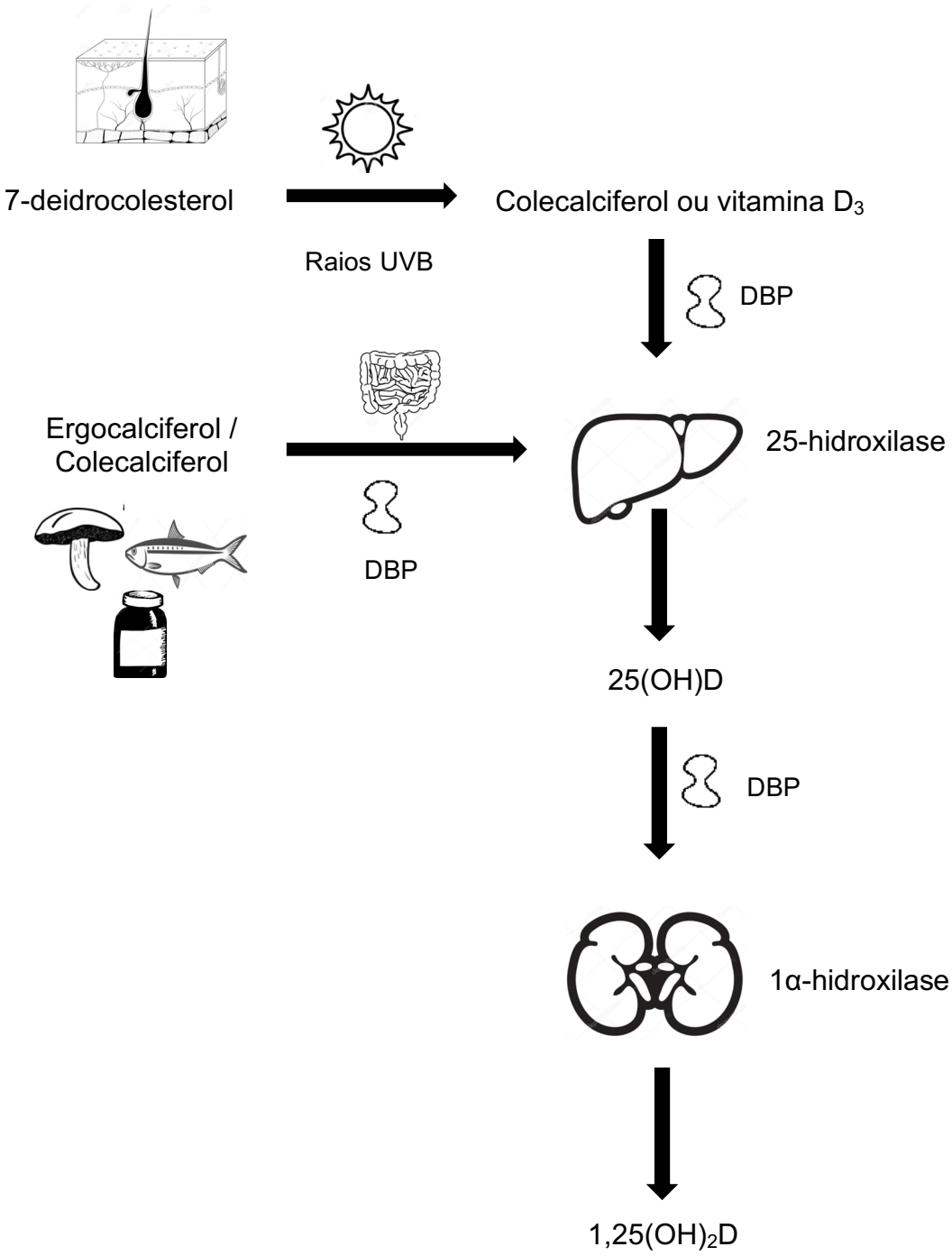
[25(OH)D], também conhecida como calcidiol. Essa é então secretada no plasma e chega nos rins, quando ocorre a segunda hidroxilação pela enzima 1α-hidroxilase (CYP27B1), formando a 1,25-dihidroxivitamina D [1,25$(OH)_2$D], chamada calcitriol. As reações de hidroxilação da vitamina D inativa é mediada pelas concentrações sérica de paratormônio (PTH), cálcio e fósforo (Figura 2) (HOLICK, 2003; LEVINE; ZAPALOWSKI; KAPPY, 2005; HEANEY et al., 2008).

Um estado estacionário é alcançado quando 10-15% do 7-DHC presente na pele é convertido em vitamina D_3, como forma de evitar toxicidade (TSIARAS; WEINSTOCK, 2011). Além disso, em condição de exposição solar excessiva, a pré-vitamina D_3 é convertida a produtos inativos, como o lumisterol e o taquisterol (KANNAN; LIM, 2014).

Outro fator de controle da intoxicação por vitamina D é o feedback negativo das enzimas 25-hidroxilase e 1α-hidroxilase, presentes no fígado e nos rins, respectivamente, e que participam da via de ativação da vitamina D, quando há um acúmulo de 25(OH)D ou de 1,25$(OH)_2$D. Além disso, o excesso de 25(OH)D e de 1,25$(OH)_2$D é metabolizado pela enzima 25-hidroxivitamina D_3-24-hidroxilase (24-OHase ou CYP24A1) e excretado pela bile (DELUCA, 2014).

Em relação à conversão da vitamina D em sua forma ativa, a partir dessa reação são produzidos metabólitos com diversas ações no organismo (SLOMINSKI et al., 2016; 2017).

Figura 2. Fotobiossíntese da vitamina D e conversão em sua forma ativa.



DBP: Proteína ligante da vitamina D

Fonte: Adaptado de Maeda et al. (2014).

2.4 METABÓLITOS DA VITAMINA D

Há mais de 20 anos estuda-se o papel da vitamina D na modulação parcial de genes codificadores de proteínas relacionadas a proliferação, diferenciação e apoptose celular (JONES; STRUGNELL; DELUCA, 1998; JURUTKA et al., 2001). Diversos tecidos e células apresentam atividade da enzima 1α-hidroxilase e a produção local de $1,25(OH)_2D$ poderia ser a responsável pela regulação de até 200 genes diferentes e que levariam a inúmeros benefícios à saúde (NAGPAL; NA; RATHNACHALAM, 2005).

Existem cerca de 41 metabólitos da vitamina D, que se ligam ao fator de transcrição nuclear VDR (*vitamin D receptor*) encontrado em locais como o intestino, rins, glândula paratireoide e osso (WANG; ZHU; DELUCA, 2012).

A vitamina D tem como papel regular não só a função celular de diversos tecidos do organismo, mas também a transcrição gênica. Sugere-se que 3% do genoma humano sofra influência da vitamina D (BOUILLON et al., 2008).

Estudos recentes tem demonstrado que não apenas a fórmula molecular $1,25(OH)_2D$ é a única a produzir benefícios ao organismo, mas também a 17(OH)D, 20(OH)D, 22(OH)D, $20,22(OH)_2D$, $20,23(OH)_2D$ e $17,20,23(OH)_3D$, que seriam convertidas a partir da vitamina D_3 pela ação do citrocromo P450scc (CYP11A1). Essas moléculas biologicamente ativas se ligam ao VDR e seriam responsáveis por diversas ações extra-ósseas, como atividade anti-tumoral e anti-inflamatória (SLOMINSKI et al., 2016; 2017).

Todos os metabólitos da vitamina D são produzidos no organismo independente do meio de aquisição da sua forma inativa (exposição solar, ingestão de suplementos ou fontes alimentares) (HOLICK, 2006).

2.5 RECOMENDAÇÕES NUTRICIONAIS E FONTES ALIMENTARES

As recomendações diárias de ingestão da vitamina D são baseadas em dados da relação entre a quantidade consumida e a saúde óssea da população norte-americana, e a ingestão diária máxima baseada em estudos que avaliaram o seu consumo associado a sinais de intoxicação (Quadro 1) (INSTITUTE OF MEDICINE, 2011).

Quadro 1. Valores de referência de ingestão diária de vitamina D para indivíduos de 0 a 18 anos.

Idade	Ingestão diária recomendada (RDA) (UI/dia)[1]	Ingestão máxima tolerada (UL) (UI/dia)[2]
0-6 meses	*	1000
6-12 meses	*	1500
1-3 anos	600	2500
4-8 anos	600	3000
9-13 anos	600	4000
14-18 anos	600	4000

* A ingestão diária recomendada não é definida, apenas a ingestão adequada (AI – adequate intake) que é de 400 UI/dia.

[1] Recommended Dietary Allowances (RDA).

[2] Upper Level Intake (UL).

UI: unidades internacionais.

Fonte: Institute of Medicine, 2011.

Há poucas fontes alimentares de vitamina D, sendo algumas delas a gema do ovo, fígado, óleo de fígado de peixe, salmão, sardinha e atum (Quadro 2) (UNITED STATES DEPARTMENT OF AGRICULTURE, 2018). Pelo fato de poucos alimentos apresentarem naturalmente vitamina D, muitos produtos alimentícios são fortificados industrialmente, como cereais matinais, leites e iogurtes (HOLICK, 2006).

Vale acrescentar que distúrbios como a intolerância à lactose e alergia à proteína do leite de vaca, e práticas alimentares como o ovo-lacto-vegetarianismo e veganismo podem reduzir o consumo de vitamina D via alimentação (INSTITUTE OF MEDICINE, 2011).

Quadro 2. Quantidade de vitamina D em alguns alimentos.

Alimento	Quantidade por porção (UI)	%VD
Oleo de fígado de bacalhau, 1 colher de sopa	1360	340
Peixe-espada, cozido, 85g	566	142
Salmao, cozido, 85g	447	112
Atum, enlatado em água, 85g	154	39
Sardinha, enlatada em óleo, 2 unidades	46	12
Figado, cozido, 85g	42	11
Ovo, 1 unidade grande (a vitamina D é encontrada na gema)	41	10
Queijo suico, 25g	6	2
Manteiga, 10g	3,5	0,9
Leite de vaca, 1L	3-40	0,8-10
Shitake fresco, 10g	10	2,5
Queijo parmesão, 10g	2,8	0,7
Camarão, 100g	152	38
Iogurte, 100g	89	22,2

UI: Unidades Internacionais.

%VD: percentual de valor diário de referência considerando a recomendação de 400 UI/dia para criancas a partir de 4 anos e adultos.

Fonte: United States Department of Agriculture, 2018; 2019.

Aproximadamente 99% dos adolescentes, adultos e idosos brasileiros apresentam inadequação no consumo de vitamina D (INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA, 2011), e um dos fatores que influenciam nos valores séricos desse nutriente é a alimentação.

2.6 AVALIAÇÃO SÉRICA

A 25(OH)D é o metabólito inativo de maior concentração no sangue, sendo este o marcador do status de vitamina D (TSIARAS; WEINSTOCK, 2011). Apesar de ser biologicamente ativa, a $1,25(OH)_2D$ não é a forma mais adequada para avaliar a dosagem sérica de vitamina D por diversos motivos: apresenta meia vida curta (4-6 horas) enquanto a da 25(OH)D é de 2 semanas (HOLICK, 2003; JONES, 2008); a concentração sanguínea de calcidiol é aproximadamente 1000 vezes maior quando comparado ao calcitriol (HOLICK, 2003); os níveis de $1,25(OH)_2D$ não são regulados pela ingestão de vitamina D, mas pela concentração da 25(OH)D e do PTH (LEVINE; ZAPALOWSKI; KAPPY, 2005); e a hidroxilação da 25(OH)D ocorre em diversos tecidos, suprindo localmente as exigências de $1,25(OH)_2D$ (ZEHNDER et al., 2001).

Quanto às metodologias para a análise sérica da vitamina D, os procedimentos de radioimunoensaio (RIA), cromatografia líquida de alta resolução (HPLC) e a cromatografia líquida acoplada à espectrometria de massas são os mais confiáveis (HOLICK, 2009), sendo a última considerada padrão ouro devido a sua maior precisão (CARTER et al., 2010).

Os níveis séricos recomendados de 25(OH)D estão apresentados no quadro 3.

Quadro 3. Recomendações do status sérico de 25(OH)D, em nmol/L, para todas as faixas etárias.

	AAP, IOM	Endocrine Society Clinical Practice Guidelines
Deficiência severa	< 12,5	-
Deficiência leve a moderada	12,5-37,5	< 50
Insuficiência	40-50	52,5-72,5
Suficiência	52,5-250	75-250
Excesso	252,5-372,5	-
Intoxicação	> 375	-

AAP: American Academy of Pediatrics; IOM: Instutute of Medicine.
Fonte: Misra et al. (2008), Institute of Medicine (2011), Holick et al. (2011).

Na infância, os sinais e sintomas da deficiência de vitamina D estão relacionados ao metabolismo do cálcio, com consequente prejuízo na estrutura óssea, e podem se manifestar de médio a longo prazo, dependendo do nível de deficiência, quantidade de ingestão de cálcio e velocidade de crescimento da criança (SOCIEDADE BRASILEIRA DE PEDIATRIA, 2014).

Dentre as causas de deficiência da vitamina D estão o baixo consumo de fontes alimentares; redução da síntese pela pele devido ao uso de protetor solar, por exemplo, um fator de proteção solar (FPS) 30 impede a absorção de 95-98% os raios solares UVB (HOLICK, 2006); a idade cronológica; a quantidade de melanina; a má absorção intestinal pela redução na absorção de gordura (em casos como a doença de Crohn, fibrose cística, etc); disfunção hepática e/ou renal, prejudicando a conversão em sua forma ativa; necessidade aumentada por alguma condição fisiológica; e as alterações genéticas como a mutação no gene receptor de vitamina D ou da enzima 1α-hidroxilase (CYP27B1) (HOLICK, 2007; HOLICK et al., 2011). Aspectos religiosos e culturais também podem interferir na produção endógena em detrimento do uso contínuo de roupas que cobrem todo o corpo, impedindo o contato da pele com o sol (OMAR et al., 2018).

Por outro lado, a toxicidade por vitamina D pode levar a hipercalcemia e/ou hipercalciúria, aumentando a deposição de cálcio e fosfato no osso e inibindo a produção de PTH (RITTER; BROWN, 2011; GALLAGHER; SMITH; YALAMANCHILL, 2014), além de provocar arritmias cardíacas, calcificação dos vasos sanguíneos, cálculo renal e nefrocalcinose (BROWN et al., 2015; KETHA et al., 2015).

Os pontos de corte da recomendação sérica de 25(OH)D foram estabelecidos em estudos com adultos e em países ocidentais com elevada prevalência de população idosa, sem considerar diferentes grupos étnicos, tornando as orientações em nível global pouco consistentes (FULEIHAN; RAHME; BASSIL, 2013). Recomendações voltadas para grupos específicos, considerando sua localização geográfica e padrão alimentar, seria o mais indicado para garantir que todos os indivíduos apresentassem concentrações adequadas de vitamina D (MENDES et al., 2018).

Mais especificamente em relação à população infantil, a quantidade de 25(OH)D para definição de hipovitaminose sérica ainda precisa ser melhor estudada, visto que o crescimento, desenvolvimento e formação óssea próprios dessa fase da vida podem requerer valores de 25(OH)D diferente das demais faixas etárias. Logo, o uso de recomendações obtidas a partir de estudos realizados com adultos pode levar a práticas clínicas inadequadas para crianças (ALONSO; MANTECÓN; SANTOS, 2019).

2.7 PREVALÊNCIA DE HIPOVITAMINOSE D

A deficiência de vitamina D é um problema mundial. Em 2007, estimou-se que um bilhão de pessoas no mundo era deficiente ou insuficiente em vitamina D (HOLICK, 2007).

Tanto em países desenvolvidos quanto em desenvolvimento, a maioria da população apresenta valores séricos de vitamina D inadequados (ROTH et al., 2018).

Entre crianças de 0-24 meses, a prevalência de deficiência de vitamina D no mundo pode variar de 13-45% (CARPENTER et al., 2012; GRANT et al., 2009; HALICIOGLU et al., 2012; LOURENÇO et al., 2019). Em 2012, foi

identificado que aproximadamente 80% dos adolescentes europeus apresentavam níveis séricos de vitamina D insuficientes (GONZÁLEZ-GROSS et al., 2012). Ainda na Europa, um estudo com 55844 indivíduos de 1,5-91 anos de idade encontrou uma prevalência de 40,4% de deficiência de vitamina D (CASHMAN et al., 2016).

Em um estudo norte-americano realizado com adultos e idosos, a prevalência de deficiência encontrada foi de 25% (SCHLEICHER et al., 2016).

No Brasil, uma pesquisa em São Paulo com mais de 39000 indivíduos de 2-95 anos identificou que 33,9% apresentaram deficiência de vitamina D (< 50 nmol/L) e 70,7% apresentaram valores séricos insuficientes (52,5-72,5 nmol/L) (ELOI et al., 2016). Considerando todas as regiões brasileiras, uma meta-análise revelou que entre os anos 2000 e 2017 a prevalência média de deficiência e insuficiência de vitamina D, na população geral, foi de 28,16% e 45,26%, respectivamente, e entre as crianças essa prevalência foi de 22,95% e 44,04%, respectivamente. Os autores atribuíram as prevalências encontradas no Brasil, semelhante à de outros países, à utilização de técnicas de redução à exposição solar, como a realização diária de atividades em ambientes fechados e o uso de protetor solar (PEREIRA-SANTOS et al., 2018).

Em países como o Canadá e a Alemanha é comum a ocorrência de deficiência de vitamina D na população em geral (JANZ; PEARSON, 2013; RABENBERG et al., 2015). Um dos motivos é o fato desses países localizarem-se em latitudes ao norte, onde há um maior período do ano em que os raios UVB apresentam angulação oblíqua, de tal forma que são absorvidos pelo ozônio da atmosfera, dificultando a produção de vitamina D por meio da exposição solar (WEBB; KLINE; HOLICK, 1988).

A alta prevalência mundial de deficiência de vitamina D, como exposto acima, pode ter contribuído para a subestimação dos seus níveis séricos recomendados (DAWSON-HUGHES et al., 2005).

2.8 VITAMINA D E SUA RELAÇÃO COM ALGUNS FATORES DE RISCO PARA DOENÇAS CARDIOVASCULARES

2.8.1 Vitamina D e dislipidemia

A dislipidemia é definida como a alteração de um ou mais lipídeos séricos, podendo ser classificada de quatro formas: hipercolesterolemia isolada (aumento da lipoproteína de baixa densidade - LDL-c), hipertrigliceridemia isolada (aumento dos triglicerídeos - TG), hiperlipidemia mista (aumento concomitante do LDL-c e TG) e liproteína de alta densidade (HDL-c) baixa (FALUDI et al., 2017).

Alguns estudos tem demonstrado, em todas as faixas etárias, a relação entre as baixas concentrações séricas de 25(OH)D e a maior prevalência de TG, colesterol total (CT) e LDL-c elevados e baixo HDL-c (CHON et al., 2014; MIETTINEN et al., 2014; MAHAJAN; BHATIA, 2017; JIANG et al., 2019), independente da obesidade (DOLINSKY et al., 2013; KIM; JEONG, 2019).

Apesar de ainda não estar totalmente elucidado, alguns mecanismos explicam a ação da vitamina D sobre o metabolismo lipídico (JIANG et al., 2019). Baixas concentrações de vitamina D também estariam associadas a um prejuízo no funcionamento das células ß-pancreáticas, favorecendo a resistência a insulina, e da ß-oxidação nos adipócitos, aumentando os níveis de TG e a formação de novos ácidos graxos (KARNCHANASORN; OU; CHIU, 2012; LARRICK et al., 2018).

Em relação ao PTH, uma de suas ações é a redução da atividade lipolítica, o que gera aumento dos TG, e as altas concentrações de vitamina D inibiria este hormônio (SONG et al., 2012).

A vitamina D pode reduzir os valores séricos de CT pela inibição da expressão da 3-hidroxi-3-metilglutaril coenzima A redutase (HMGR), enzima que participa da biossíntese do colesterol (LI et al., 2016). Além disso, o cálcio, que tem sua absorção intestinal aumentada pela vitamina D, se ligaria aos ácidos biliares, aumentando a sua excreção, o que levaria o fígado a utilizar uma maior quantidade de colesterol para a produção da bile, reduzindo os níveis séricos de LDL-c e CT (CHRISTAKOS et al., 2011; DITSCHEID; KELLER; JAHREIS, 2005). Esse aumento da absorção do cálcio também

contribuiria para a redução serica de TG, uma vez que esse mineral diminui a sua formação e secreção hepática (CHO et al., 2005).

Quanto ao HDL-c, a ABCA1 (*ATP-binding membrane cassette transporter A1*) é um transportador lipídico que participa da sua formação, e a $1,25(OH)_2D$ induz à expressão desse transportador, contribuindo assim para o transporte reverso do colesterol (VAN ECK, 2014; YIN et al., 2015).

Em uma meta-análise recente, de estudos realizados com indivíduos com mais de 18 anos de idade, foi identificado que a suplementação de vitamina D pode reduzir os as concentrações séricas de CT, LDL-c e TG, mas não influenciar nos valores de HDL-c (DIBABA, 2019). Em outra meta-análise, de estudos conduzidos com crianças, encontrou-se uma associação inversa entre a vitamina D e os valores de TG, CT e LDL-c, e direta com o HDL-c (KELISHADI; FARAJZADEGAN; BAHREYNIAN, 2014).

2.8.2 Vitamina D e hiperglicemia

A glicemia de jejum (GJ) pode indicar pré-diabetes quando a sua concentração está ≥ 100 e < 126 mg/dL, ou diabetes ≥ 126 mg/dL (AMERICAN DIABETES ASSOCIATION, 2019a). Quando não tratada, a hiperglicemia pode levar a complicações cardiovasculares, que são as principais causas de mortalidade entre esses indivíduos (ZHENG; LEY; HU, 2018).

Dentre as ações da vitamina D sobre o metabolismo glicídico, a melhora da tolerância à glicose e da sensibilidade à insulina seriam alguns dos benefícios (ISMAIL; NAMALA, 2000). A influência da vitamina D na GJ se daria diretamente pela ligação da $1,25(OH)_2D$ na VDR presente nas células β pancreáticas, que também expressam a enzima 1α-hidroxilase (BLAND et al., 2004). A secreção de insulina é influenciada pela vitamina D visto que a sua produção é um processo cálcio-dependente, e o influxo deste mineral para as células β pancreáticas é favorecido pela $1,25(OH)_2D$ (ISMAIL; NAMALA, 2000; ZEITZ et al., 2003). Além disso, a deficiência de vitamina D parece prejudicar a conversão da pró-insulina em insulina no pâncreas (AYESHA et al., 2001).

Embora haja uma associação inversa entre os níveis séricos de 25(OH)D e o risco de desenvolvimento de DM2 (SONG et al., 2013), não há

evidências científicas suficientes que recomendem a suplementação de vitamina D para o controle da glicemia (AMERICAN DIABETES ASSOCIATION, 2019b), visto que meta-análises recentes não identificaram a associação deste nutriente com o controle glicêmico em indivíduos diabéticos (LI et al., 2018; WU et al., 2017).

2.8.3 Vitamina D e obesidade

A obesidade é um problema de saúde pública mundial, e os níveis sanguíneos de 25(OH)D parecem relacionar-se inversamente com essa condição (EARTHMAN et al., 2012; MAI et al., 2012) e com valores de circunferência da cintura (CC), percentual de gordura corporal (%GC) e dobras cutâneas (SNIJDER et al., 2005; SEO et al., 2013).

As baixas concentrações séricas de vitamina D podem ser tanto causa como consequência da obesidade. Uma das causas parece ser o estilo de vida sedentário, uma vez que contribui para que as atividades diárias sejam prioritariamente em ambientes fechados e com pouca exposição ao sol (WORLD HEALTH ORGANIZATION, 2003; RAJAKUMAR et al., 2008). A alimentação de alta densidade calórica e pobre em vitamina D também contribui para a baixa concentração sérica desse nutriente (BRADLEE et al., 2010). Outra explicação é que o excesso de gordura subcutânea, que armazena vitamina D, sequestra parte desse nutriente obtido tanto pela ingestão oral quanto pela produção endógena, impedindo que ele seja transportado para o fígado e sofra a sua primeira hidroxilação, o que pode diminuir a sua concentração sérica (WORTSMAN et al., 2000).

Como consequência, há relato de que a deficiência de vitamina D é comumente encontrada em indivíduos obesos, sendo este um dos mecanismos que contribui para o acúmulo de gordura corporal (SNIJDER et al., 2005; KIMMONS et al., 2006). Um estudo *in vitro* revelou que a $1,25(OH)_2D$ inibiria a expressão do receptor ativador de proliferação de peroxissomos γ (PPARγ), regulador-mestre da adipogênese, reduzindo assim a síntese de tecido adiposo (WOOD, 2008; CHENG et al., 2010).

Outra consequência é que o sequestro da vitamina D pelo tecido adiposo reduziria a sua concentração sérica, o que levaria a um aumento do

PTH, com consequente elevação do influxo de cálcio para os adipócitos, e este mineral reduziria a lipólise pela ativação da fosfodiesterase 3B, contribuindo para o surgimento da obesidade (KAMYCHEVA; SUNDSFJORD; JORDE, 2004; ZEMEL et al., 2000; McCARTY; THOMAS, 2003).

Deve-se considerar os fatores genéticos associados à obesidade, que podem sofrer influência dos níveis séricos de 25(OH)D. Um estudo com 796 crianças brasileiras identificou que aquelas com insuficiência de vitamina D (< 75 nmol/L) apresentaram associação do genótipo rs9939609, do *fat mass and obesity-associated gene* (FTO), com o aumento da razão índice de massa corporal(IMC)/idade (p=0,003), enquanto essa relação não foi encontrada entre crianças com níveis suficientes de 25(OH)D (p>0,05) (LOURENÇO et al., 2014).

Entre 1441 adolescentes peruanos, aqueles com excesso de peso corporal, identificado pelo IMC, apresentaram menores concentrações séricas de 25(OH)D quando comparado aos indivíduos eutróficos (p<0,001) (TOMAINO et al., 2015). Essa mesma associação foi encontrada em um estudo com 546 crianças espanholas (p = 0,001) (DURÁ-TRAVÉ et al., 2017).

Uma meta-análise de 23 estudos indicou associação entre a hipovitaminose D e o sobrepeso e a obesidade, independente da faixa etária (PEREIRA-SANTOS et al., 2015).

2.8.4 Vitamina D e hipertensão arterial sistêmica

A HAS é uma condição caracterizada pelo aumento persistente da pressão arterial sistólica (PAS) e/ou diastólica (PAD) sobre a parede dos vasos sanguíneos, também considerada um problema de saúde pública mundial (WORLD HEALTH ORGANIZATION, 2019). Quando não tratada na infância, pode levar ao desenvolvimento de DCV na vida adulta, como infarto e cardiopatia isquêmica (MAGNUSSEN; SMITH, 2016).

A insuficiência ou deficiência de vitamina D tem sido associada a uma maior chance de desenvolvimento de HAS, tanto em crianças quanto em adultos (SCRAGG; SOWERS; BELL, 2007; XU; JIN; DU, 2017).

No estudo realizado com 1441 adolescentes peruanos, foi identificada uma maior média nos valores de PAS e PAD naqueles com níveis séricos de

25(OH)D < 50 nmol/L, quando comparado aos indivíduos com valores ≥ 50 nmol/L (p<0,01 e p<0,001, respectivamente) (TOMAINO et al., 2015).

Em relação à suplementação de vitamina D, um ensaio clínico com 49 adolescentes afro-americanos normotensos e com hipovitaminose D identificou que aqueles que receberam 2000 UI/dia por 16 semanas apresentaram menor rigidez da parede arterial quando comparado àqueles que ingeriram apenas 400 UI/dia (p=0,019) (DONG et al., 2010).

Entre 7561 adultos norte-americanos foi identificado valores de PAS 3,5 mmHg superiores entre os indivíduos que apresentavam 25(OH)D < 33 nmol/L quando comparados àqueles ≥ 75 nmol/L (HE; SCRAGG, 2011).

A ação da vitamina D sobre os níveis pressóricos pode ser explicada por sua participação na regulação do sistema renina-angiotensina-aldosterona, sendo que os níveis adequados de vitamina D preveniria a sua hiperestimulação e o aumento dos valores de PAS e PAD (WILLIAMS; MALATESTA; NORRIS, 2009).

No aparelho justaglomerular, a $1,25(OH)_2D$ tem a capacidade de suprimir a expressão do gene da renina e o crescimento e proliferação de células musculares lisas vasculares (VSMC), sendo este último relacionado a hipertrofia e hiperplasia da parede vascular (MERKE et al., 1987). Além disso, a não ativação do receptor de vitamina D neste órgão pode levar a inadequação do sistema renina-angiotensina-aldosterona, contribuindo para a HAS e hipertrofia ventricular esquerda (LI et al., 2002; XIANG et al., 2005). A $1,25(OH)_2D$ também tem como função bloquear a ação dos produtos finais de glicação avançada nas células endoteliais, evitando sua disfunção e rigidez arterial (TALMOR et al.; 2008).

Quanto à exposição solar, os raios UVB podem reduzir a pressão arterial possivelmente em razão do aumento nos níveis de $1,25(OH)_2D$ (ROSTAND, 2014).

Uma meta-análise de 2017 identificou não haver associação entre a hipovitaminose D e o maior risco de desenvolvimento de HAS, sugerindo a realização de mais estudos para esclarecimento da relação entre ambos (QI et al., 2017). Porém, um estudo de randomização mendeliana encontrou que uma maior presença de alelos relacionados a síntese de 25(OH)D estava

associado a uma redução nos valores de PAS e PAD e menor probabilidade de desenvolvimento de HAS ($p < 0,05$) (VIMALESWARAN et al., 2014).

2.9 SUPLEMENTAÇÃO DE VITAMINA D

Caso a recomendação de exposição solar não seja suficiente ou possível de ser atingida pelo indivíduo, o uso de suplemento pode ser considerado para se obter níveis adequados de vitamina D (WACKER; HOLICK, 2013).

Pode-se administrar tanto o colecalciferol quanto o ergocalciferol, porém o primeiro aumenta em 2-3 vezes as concentrações séricas de 25(OH)D quando comparado ao segundo (HEANEY et al., 2011). A suplementação pode ser realizada com ou sem refeição (HOLICK et al., 2011).

Não se recomenda a suplementação de calcitriol em detrimento da sua curta meia-vida e incapacidade de elevar os estoques de vitamina D (LEE; SO; THACKRAY, 2013).

O impacto da suplementação nos níveis séricos de 25(OH)D depende de diversos fatores, como os valores basais, quantidade e duração do tratamento. Em relação a quantidade, quando a ingestão é ≥1000 UI/dia, a elevação sérica é de 1 nmol/L para cada 40 UI, e quando se ingere ≤ 600 UI/dia, o incremento é de 2,25 nmol/L para cada 40 UI administrada (HEANEY et al., 2003).

Orienta-se que, iniciada a suplementação de vitamina D, sua dosagem sérica seja realizada a cada três meses, até que os níveis adequados sejam atingidos e a suplementação interrompida (SOCIEDADE BRASILEIRA DE PEDIATRIA, 2014).

Para o aumento dos níveis séricos de vitamina D, Holick et al. (2011) sugerem para pessoas de 1-18 anos uma suplementação de 2000 UI/dia ou 50000 UI/semana, todos os dois por seis semanas ou até atingir a concentração sérica de vitamina D ≥ 75 nmol/L (Quadro 4). Contudo, a suplementação não diária de vitamina D e em doses elevadas parece ser menos efetiva na manutenção de concentrações estáveis no sangue (HOLLIS; WAGNER, 2013).

Quadro 4. Recomendação de suplementação de vitamina D para correção do seu status sérico entre indivíduos de 0 a 18 anos.

Idade em anos	Dosagem diária (UI) (por 6 semanas)	Dosagem semanal (UI) (por 6 semanas)	Dose diária de manutenção após atingir níveis ≥ 75 nmol/L
0-1	2000	50000	400-1000
1-18	2000	50000	600-1000

Fonte: Holick et al., 2011.

Diante do exposto, este trabalho mostra-se relevante na elucidação dos possíveis benefícios da suplementação de vitamina D para a saúde de crianças, mesmo entre aquelas com níveis séricos considerados suficientes, além de investigar a relação entre os níveis séricos de 25(OH)D e demais marcadores biológicos nesta população. Ainda, esta pesquisa justifica-se pela importância da promoção da saúde na idade pediátrica e pela necessidade de mais estudos que contribuam para o retardo ou prevenção do desenvolvimento de condições fisiológicas que são fatores de risco para doenças crônicas não transmissíveis.

3 OBJETIVOS

3.1 OBJETIVO GERAL

Avaliar os níveis séricos e o efeito da suplementação de vitamina D sobre a composição corporal e perfil metabólico de crianças.

3.2 OBJETIVOS ESPECÍFICOS

- Caracterizar o perfil sociodemográfico, econômico e o estilo de vida de crianças de uma instituição pública de ensino;
- Comparar dados da antropometria, composição corporal e perfil metabólico de crianças de uma instituição pública de ensino, de acordo com os níveis séricos de 25(OH)D;
- Comparar o consumo alimentar, antropometria, composição corporal e variáveis metabólicas dos grupos suplementados com colecalciferol e placebo antes e após a intervenção.

4 MÉTODOS

Este estudo faz parte de um projeto maior, denominado “Síndrome metabólica: respostas metabólicas, oxidativas e inflamatórias de programas de exercício físico e nutricional em escolares de quatro a 11 anos do município de Santo Antônio de Goiás”, iniciado em 2017 e ainda em vigência.

4.1 TIPO E LOCAL DO ESTUDO

Foi realizado um ensaio clínico randomizado, placebo-controlado, triplo-cego, cruzado (*crossover*) com duração de 34 semanas, com crianças de uma escola pública municipal da cidade de Santo Antônio de Goiás, situada a 13 km de distância da capital do estado de Goiás, Goiânia, e ocupa uma área de 132,80 km^2 (IBGE, 2019).

4.2 POPULAÇÃO E CRITÉRIOS DE SELEÇÃO DOS PARTICIPANTES

De acordo com dados do Instituto Brasileiro de Geografia e Estatística, em 2019, a população de Santo Antônio de Goiás foi estimada em 6283 habitantes e dados de 2017 informaram que 1148 crianças estavam matriculadas no ensino fundamental e infantil (IBGE, 2019). No entanto, de acordo com dados da Secretaria Municipal de Educação, o número de crianças de quatro a 11 anos de idade matriculadas na Escola Municipal Professora Uberaciema Vanuncio, de Santo Antônio de Goiás, em 2017, era de 1069 crianças.

A seleção dos participantes seguiu os seguintes critérios de inclusão: ter idade entre quatro e 11 anos, possuir concentrações séricas de 25(OH)D suficientes (≥ 75 nmol/L) (para o estudo transversal) e apresentar hipertrigliceridemia (TG ≥ 75 mg/dL e ≥ 90 mg/dL entre crianças de 0-9 anos e ≥ 10 anos, respectivamente) (para o estudo *crossover*) (HOLICK et al., 2011;

FALUDI et al., 2017). Como critérios de exclusão considerou-se crianças com deficiência física ou cognitiva que comprometesse a coleta de dados, e adicionalmente para o estudo *crossover* foram excluídas aquelas com alguma doença crônica diagnosticada (hipertensão arterial sistêmica, diabetes mellitus, doença renal, hepática, cardiovascular, auto-imune), em acompanhamento nutricional, em uso de algum medicamento que influenciasse na composição corporal, pressão arterial ou na concentração sérica das lipoproteínas e glicemia e que houvesse utilizado suplemento de colecalciferol nas últimas 10 semanas.

4.3 AMOSTRA

O recrutamento das crianças ocorreu por intermédio da direção da escola de ensino básico do município, onde foi cedido um momento para apresentação do projeto de pesquisa e esclarecimentos dos procedimentos metodológico, durante duas reuniões pré-agendadas pela escola com os pais ou responsáveis pelas crianças.

Foram registrados o contato dos pais ou responsáveis legais, que manifestaram interesse na participação de seus filhos na pesquisa, para agendamento das coletas de dados na Unidade Básica de Saúde (UBS) do município e para a assinatura dos Termos de Consentimento (TCLE) e Assentimento (TALE) Livre e Esclarecido (Apêndice 1).

Após a aplicação dos critérios de seleção, foram incluídas no estudo transversal 88 crianças (39 meninas e 49 meninos) e no ensaio clínico 62 crianças (31 meninas e 31 meninos) (Figura 3).

Das 101 crianças avaliadas para alegibilidade, 39 não se encaixaram nos critérios de inclusão do ensaio clinico. Desta forma, 62 crianças foram alocadas de forma randomizada, sendo 31 no grupo suplementado e 31 no grupo placebo. A randomização foi realizada de forma estratificada, visando eliminar possíveis vieses ao distribuir de maneira semelhante variáveis que poderiam configurar fator de confusão entre os dois grupos [sexo, idade, massa corporal, estatura, 25(OH)D e lipoproteínas séricas]. Durante o período de intervenção, houve perda amostral de oito crianças no grupo suplementado

(GS) e dez crianças no grupo placebo (GP), totalizando uma amostra final de 49 crianças. Destas, foram incluídas na análise estatística apenas as crianças que consumiram pelo menos 80% da suplementação esperada (ASSOCIAÇÃO MÉDICA BRASILEIRA, 2009; ELLIS et al., 2000), resultando em um número final de 44 participantes (Figura 4).

Os dados de linha de base (n=88), obtidos a partir da fase de seleção para o ensaio clínico, foram utilizados para o estudo transversal e originou o artigo 1 desta Tese. Nesta etapa, dados de 13 crianças não foram utilizados por apresentarem nível sérico de 25(OH)D < 75 nmol/L. O tamanho da amostra (n=88) que integrou o estudo tem poder amostral de 0,80, $\alpha = 0,05$, $\beta = 0,20$ e tamanho de efeito de 0,54, obtido a partir o teste de t não pareado e tipo de poder de análise "*a priori: compute required sample size – given α, power and effect size"*, realizado no programa G*Power versão 3.1.

Os dados da intervenção (*crossover*) deram origem ao artigo 2 desta Tese. Para o cálculo amostral, também realizado no software G-Power® versão 3.1, foram considerados os valores de TG sérico de crianças suplementadas com vitamina D no estudo de Nader et al. (2014) (grupo placebo 106,3±47,2 mg/dL e grupo suplementado 132,5±63,8 mg/dL). Considerando o teste de t pareado e tipo de poder de análise "*a priori: compute required sample size – given α, power and effect size",* seria necessária uma amostra de 14 indivíduos, com um tamanho de efeito de 0,46, poder estatístico de 80% e erro amostral de 20%. Estimando-se possíveis perdas, foram incluídas um total de 62 crianças, finalizando o estudo 44 participantes, o que representou uma perda de 29% e um estudo com tamanho de efeito de 0,26, poder estatístico de 80% e erro amostral de 20%.

Figura 3. Fluxograma de recrutamento dos participantes para os estudos transversal e ensaio clínico.

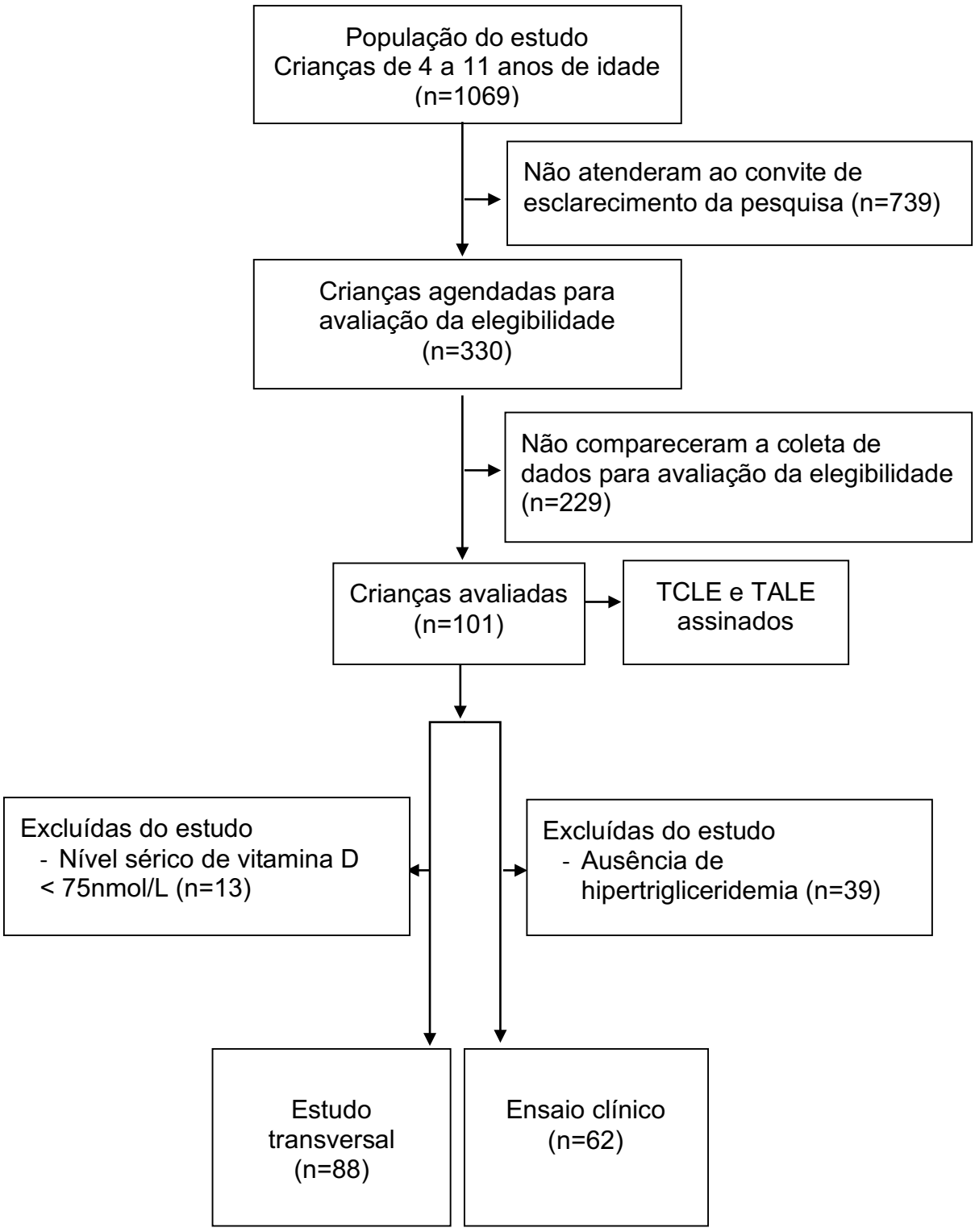
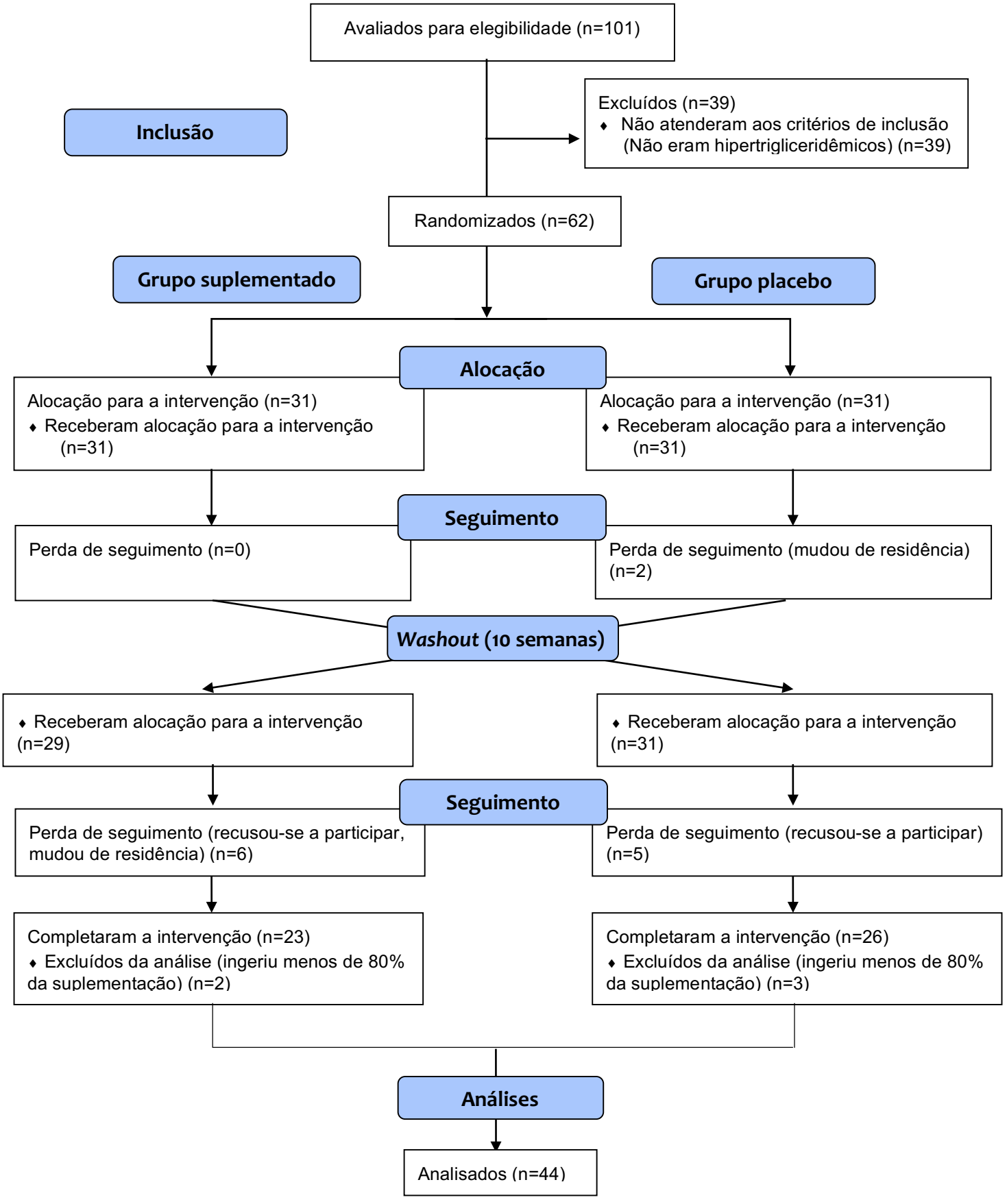


Figura 4. Fluxograma dos participantes ao longo do ensaio clínico.



4.4 COLETA DE DADOS

Anteriormente à coleta de dados, foi realizado treinamento teórico e prático dos acadêmicos dos cursos de Nutrição e Educação Física e do Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Goiás (UFG) que auxiliaram no desenvolvimento da pesquisa. O treinamento incluiu a aplicação de questionário sóciodemográfico e econômico, uso de protetor solar e percentual da área corporal normalmente exposta ao sol, prática de atividade física, recordatório de 24 horas, aferição da pressão arterial, medidas antropométricas e composição corporal.

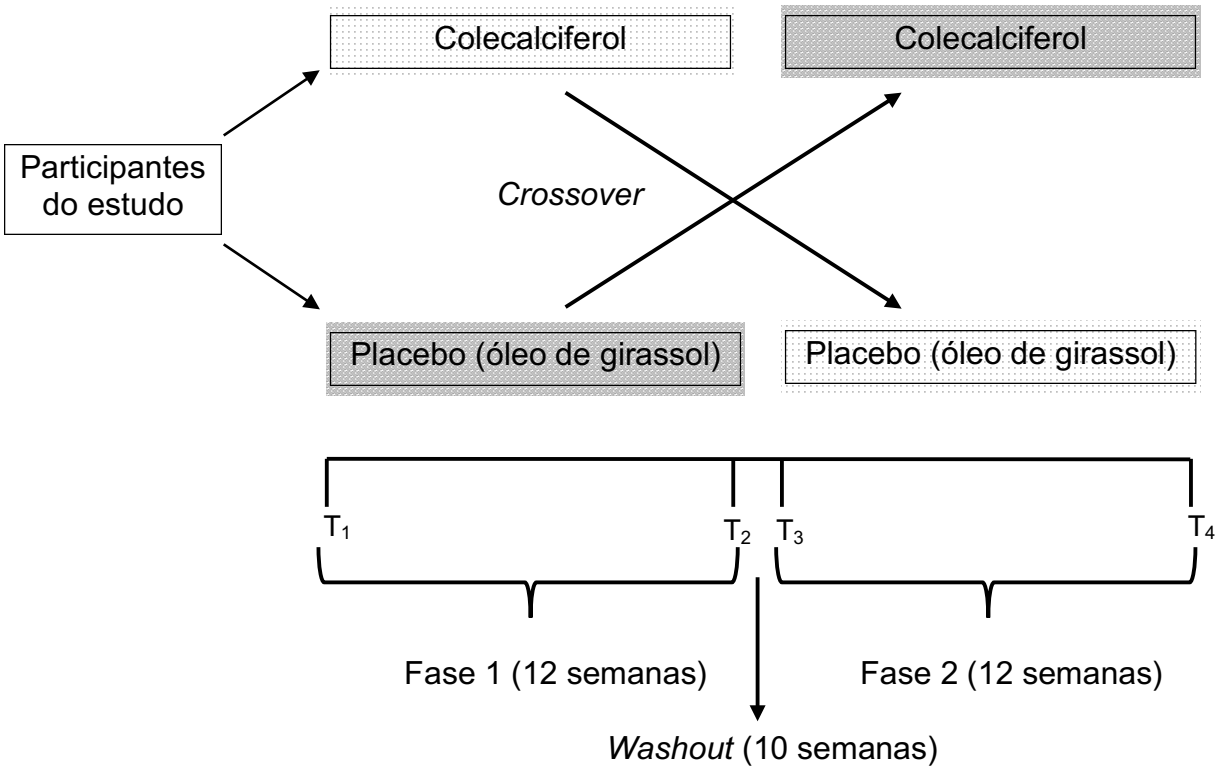
A coleta de dados, que ocorreu entre setembro de 2017 e dezembro de 2018 com o apoio das Secretarias de Educação e de Saúde do município, foi realizada em dois momentos. No primeiro, os dados foram obtidos de forma transversal, e no segundo momento procedeu-se o ensaio clínico randomizado.

A pesquisa foi estratificada em duas etapas, cada uma com duração de 12 semanas, separadas por um intervalo de 10 semanas (*washout*), tempo este estabelecido pela *United States Food and Drug Administration guidelines* (2013), que preconiza que o período de *washout*, para eliminar os possíveis efeitos residuais (*carryover*) da primeira fase, deve ser equivalente a cinco vezes o tempo de meia-vida da substância administrada para a eliminação de mais de 95% pelo organismo e, no caso da 25(OH)D, a meia-vida é de aproximadamente 2 semanas (JONES, 2008; FOOD AND DRUG ADMINISTRATION, 2013). A duração de 12 semanas de suplementação com 1000 UI/dia de colecalciferol, para todas as crianças, foi utilizada por ser o período recomendado para que ocorra a elevação nos níveis séricos de 25(OH)D ≥ 75 nmol/L (PRAMYOTHIN; HOLICK, 2012).

A coleta de dados sobre o consumo alimentar, aferição da pressão arterial, avaliação da composição corporal e análise bioquímica ocorreu no início e no final de cada fase do *crossover* (Figura 5).

Durante o período de intervenção, os pais ou responsáveis foram orientados a não modificar os hábitos alimentares, prática de atividade física e métodos de proteção e exposição solar habituais das crianças.

Figura 5. Etapas do ensaio clínico.



T_1, T_2, T_3 e T_4: Avaliação do consumo alimentar, pressão arterial, composição corporal e análise bioquímica.

4.5 INTERVENÇÃO

Os GS e GP receberam, por 12 semanas cada, cinco gotas de colecalciferol em veículo oleoso (óleo de girassol), equivalente a 1000 UI/dia, e cinco gotas de óleo de girassol, direto na boca e com o uso de conta-gotas, após o almoço, respectivamente. Esse horário foi estabelecido para padronização do momento de ingestão do suplemento de vitamina D e placebo por todas as crianças. Visando maior controle dessa administração, foram entregues fichas para o preenchimento do horário em que as crianças recebiam os mesmos (Apêndice 2), além do envio semanal de mensagens via celular.

Os pais ou responsáveis foram informados que as crianças receberiam o suplemento de vitamina D por um período total de 24 semanas, não sendo

relatado sobre a administração do placebo. Nos frascos continham informações sobre o seu correto armazenamento (temperatura ambiente, em local seco, arejado e não exposto ao sol).

A posologia de 1000 UI foi estabelecida por esta ser uma quantidade mínima necessária de suplementação diária para a elevação dos níveis séricos de 25-hidroxivitamina D acima de 75 nmol/L, além de ser uma dosagem considerada segura para suplementação entre as crianças (inclusive para a manutenção dos níveis séricos adequados) e não ultrapassar a quantidade máxima de ingestão diária permitida (3000 UI entre 4-8 anos e 4000 UI entre 9-13 anos de idade) (PRAMYOTHIN; HOLICK, 2012; INSTITUTE OF MEDICINE, 2011).

4.6 ASPECTOS ÉTICOS

Esta pesquisa foi aprovada pelo Comitê de Ética em Pesquisa da UFG, parecer nº 1.970.935 e Certificado de Apresentação para Apreciação Ética (CAAE) nº 62297616.7.0000.5083 (Anexo 1).

O projeto foi apresentado ao prefeito do município de Santo Antônio de Goiás, juntamente com representantes das Secretarias de Educação e de Saúde, para apreciação e aprovação do mesmo e organização da logística sobre onde ocorreriam as coletas de dados.

Todos os pais ou responsáveis, antes da assinatura dos TCLE e TALE, foram informados sobre todas as etapas da pesquisa, bem como o seu objetivo, o sigilo dos dados coletados, sua divulgação para a prefeitura do município e publicação acadêmica, além da possibilidade de desistência a qualquer momento, sem nenhum prejuízo.

O ensaio clínico foi registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC), com *Universal Trial Number* (UTN) U1111-1214-5845.

Por se tratar de uma pesquisa envolvendo seres humanos, todos os procedimentos metodológicos seguiram as recomendações da resolução 466/2012 do Conselho Nacional de Saúde.

4.7 PROTOCOLOS DE AVALIAÇÃO

4.7.1 Caracterização social, demográfica e econômica

No primeiro encontro (T_1), agendado na UBS do município, após as assinaturas dos TCLE e TALE, foram coletados os dados sociodemográficos e econômicos (sexo, data de nascimento, raça, renda familiar, número de membros da família que residem juntos) a partir de questionário especifico (Apêndice 3).

4.7.2 Exposição solar

Os pais/responsáveis e a criança, em T_1, pintaram uma figura contendo as partes do corpo do avaliado que representava a área corporal exposta diariamente ao sol, além de informarem quanto ao uso de protetor solar (Apêndice 4). A figura representativa da área corporal foi baseada na publicação de Yin (2017), que retrata o percentual de cada parte do corpo, de acordo com a faixa etária (Quadro 5). A partir desses dados, foi calculado o percentual corporal total da criança que diariamente ficava exposto ao sol.

Quadro 5. Percentual relativo das áreas afetadas pelo crescimento.

	Idade em anos					
	0	1	5	10	15	Adulto
A/D – ½ da cabeça	9 ½	8 ½	6 ½	5 ½	4 ½	3 ½
B/E – ½ da coxa	2 ¾	3 ¼	4	4 ½	4 ½	4 ¾
C/F – ½ da perna	2 ½	2 ½	2 ¾	3	3 ¼	3 ½

Fonte: Yin, 2017.

4.7.3 Prática de atividade física

A avaliação da prática de atividade física entre as crianças, em T_1, foi realizada por meio da aplicação de questionário proposto por Oliveira et al. (2011) (Anexo 2).

Esse questionário é composto por quatro perguntas, duas relacionadas ao tempo gasto com brincadeiras ou jogos ao ar livre e outras duas em relação ao tempo assistindo televisão. Cada pergunta possui três tópicos, referentes ao período do dia (manhã, tarde e noite), e cada um desses períodos são divididos em minutos. A pontuação para as perguntas sobre o tempo gasto com brincadeiras ou jogos ao ar livre são em ordem crescente: 0 para 0 minutos, 1 para 1-15 minutos, 2 para 16-30 minutos, 3 para 31-60 minutos e 4 para > 60 minutos. Para as perguntas sobre o tempo assistindo televisão, a pontuação é invertida (quanto maior o tempo é atribuído pontuação menor). A classificação da prática de atividade física foi dividida em ativo, quando a soma de toda a pontuação equivalesse a pelo menos 60 minutos/dia de prática de atividade física, e pouco ativo, quando esse tempo fosse < 60 minutos/dia (OLIVEIRA et al., 2011).

4.7.4 Composição corporal

A composição corporal foi aferida em T_1, T_2, T_3 e T_4, e as variáveis analisadas foram o IMC, CC, relação cintura-estatura (RCE), gordural corporal e massa livre de gordura (MLG).

4.7.4.1 Índice de massa coporal

O IMC foi calculado por meio da divisão da massa corporal (kg) pelo quadrado da estatura (m).

A massa corporal foi aferida em balança eletrônica Seca® (modelo 813, Hamburgo, Alemanha), com capacidade de 200 kg e precisão de 100 g, com a criança vestindo o mínimo de roupa possível. Para a aferição da estatura foi utilizado o estadiômetro portátil Seca® (modelo 213, Hamburgo, Alemanha), graduado em milímetros e com medição máxima de 205 cm. Para a coleta de ambos, os participantes foram orientados a ficar em posição ortostática, descalços, com a cabeça ereta e sem acessórios, além dos braços estendidos.

A classificação do IMC foi realizada segundo o percentil IMC/idade (Quadro 6), cujos gráficos diferem por sexo e faixa etária (WORLD HEALTH ORGANIZATION, 2007).

Quadro 6. Classificação IMC/idade para crianças e adolescentes.

Percentil IMC/idade	Diagnóstico Nutricional
< Percentil 3	Magreza
≥ Percentil 3 e ≤ Percentil 85	Eutrofia
> Percentil 85 e ≤ Percentil 97	Sobrepeso
> Percentil 97	Obesidade

Fonte: World Health Organization, 2007.

4.7.4.2 Circunferência da cintura

A CC foi aferida em duplicata no ponto médio entre a porção inferior da última costela e a crista ilíaca (INTERNATIONAL SOCIETY FOR ADVANCEMENT OF KINANTHROPOMETRY, 2011), e para isso foi utilizada uma fita antropométrica inextensível da marca Cescorf® (Porto Alegre, Brasil).

A classificação da CC seguiu as recomedações de Fernández et al. (2004), cujos valores de percentis da CC encontram-se em tabelas estratificadas por sexo e faixa etária. Valores de CC ≥ percentil 75 foram considerados como elevados.

A RCE foi obtida por meio da divisão da CC pela estatura, ambos em centímetros, e foi categorizada em < 0,5 como normal e ≥ 0,5 como aumentada para todas as faixas etárias (STUPNICKI et al., 2013).

4.7.4.3 Gordura corporal e massa livre de gordura

O %GC e a MLG foram determinados a partir dos valores de resistência e reactância obtidos por meio de bioimpedância tetrapolar (*Bioelectrical Impedance Analyzer*, RJL Systems®, modelo Quantum II, Michigan, Estados Unidos da América). A partir de *software online* da RJL Systems® foram analisados os valores obtidos. Para a realização do exame, as crianças seguiram as recomendações dispostas no Quadro 7.

Quadro 7. Preparação para a realização da bioimpedância.

1. Não ter se exercitado ou feito sauna 8 horas antes do teste. 2. Não ir ao exame suado ou com hidratante na pele. 3. Não estar com febre. 4. No momento de exame, retirar sapatos, meias e acessórios metalizados. 5. Avisar caso possua marca-passo.

Fonte: RJL Systems, 2007.

A classificação do %GC seguiu as curvas de referência estabelecidas por McCarthy e colaboradores (2006), estratificadas por sexo e faixa etária, cujos valores de %GC ≤ percentil 2 refere-se a baixa gordura corporal, ≥ percentil 85 e < percentil 95 sobrepeso, e ≥ percentil 95 indicativo de obesidade.

As dobras cutâneas tricipital (DCT) e subescapular (DCSE) foram mensuradas com o adipômetro Lange® (Beta Technology, Santa Cruz, Estados Unidos da América), cujos valores foram obtidos pela média de duas aferições. A DCT foi aferida com o avaliador posicionado atrás do avaliado, verticalmente na superfície mais posterior do braço, na linha correspondente ao ponto médio entre o acrômio e o rádio. A DCSE, com o avaliador também atrás da criança, foi medida no local marcado 2 cm ao longo da linha que desce lateral e obliquamente, a partir do ângulo inferior da escápula em um ângulo de 45° (INTERNATIONAL SOCIETY FOR ADVANCEMENT OF KINANTHROPOMETRY, 2011).

4.7.5 Parâmetros metabólicos

4.7.5.1Pressão arterial

A pressão arterial dos participantes foi aferida em T_1, T_2, T_3 e T_4. Uma sala da UBS foi separada exclusivamente para este fim e, para a correta técnica de mensuração, foram consideradas as recomendações preconizadas pela Sociedade Brasileira de Cardiologia (Quadro 8) (MALACHIAS et al., 2016).

Quadro 8. Condições padronizadas para a aferição da pressão arterial em crianças.

1. Local do exame: calmo e com temperatura agradável, contribuindo para o relaxamento da criança.
2. Pedir para a criança sentar, com as pernas descruzadas, em uma cadeira e descansar por 5 minutos.
3. Relatar à criança e seu responsável como se dará o procedimento.
4. Perguntar se a criança está com a bexiga cheia e, em caso afirmativo, pedir para urinar antes da aferição.
5. Garantir que a criança não praticou exercício físico intenso ou ingeriu alguma bebida ou alimento com cafeína 60 minutos antes da aferição.
6. Deixar o braço direito livre de vestimenta, de forma que esta não aperte o membro.
7. Posicionar o braço na altura do coração, apoiado, com a palma da mão voltada para cima.
8. Realizar a segunda medição após um minuto do término da primeira.
9. Considerar a média de duas aferições, sendo que uma terceira deve ser realizada caso as duas primeiras forem muito diferentes.

Fonte: Malachias et al., 2016.

A aferição da pressão arterial foi realizada com o monitor digital automático profissional Omron® (modelo HBP-1100, Hoofddorp, Holanda), de acordo com as instruções contidas no manual. O tamanho da braçadeira foi escolhido de acordo com o tamanho da circunferência do braço da criança, sendo que esta foi obtida no braço direito no ponto acromial radial médio, perpendicular ao eixo do úmero (INTERNATIONAL SOCIETY FOR ADVANCEMENT OF KINANTHROPOMETRY, 2011).

Para a classificação dos valores de PAS e PAD, foram considerados os percentis de PAS e PAD de acordo com a estatura e sexo, cujas áreas sombreadas nos dois gráficos estavam divididas em cinco categorias: hipotensão (abaixo do percentil 5 ou 90/50 mmHg), pressão arterial normal (entre os percentis 5 e 90), pré-hipertensão (acima do percentil 90 ou 120/80 mmHg e abaixo do percentil 95), hipertensão estágio 1 (acima do percentil 95

e abaixo do percentil 99 + 5 mmHg) e hipertensão estágio 2 (acima do percentil 99 + 5 mmHg) (BANKER et al., 2016).

Foram consideradas hipertensas as crianças que apresentaram PAS e/ou PAD superior ao percentil 95 em pelo menos três ocasiões distintas (UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, 2004) que, no caso desta pesquisa, foram avaliados os quatro momentos em que houve a aferição.

4.7.5.2 Variáveis bioquímicas

A coleta de sangue foi realizada no período da manhã, por técnicas em enfermagem da UBS do município. Os pais ou responsáveis foram orientados a manter as crianças em jejum de no mínimo oito e no máximo 12 horas, com alimentação habitual no dia anterior.

Por meio de punção venosa, obteve-se 8 mL de sangue em tubo contendo gel separador para a análise do perfil lipídico (CT, LDL-c, HDL-c, não HDL-c e TG) e 25(OH)D, e 3 mL de sangue foram coletados em tubo contendo fluoreto de sódio para obtenção da GJ. Os tubos foram centrifugados a 4000 RPM por doze minutos e transportados em caixa térmica refrigerada ao Laboratório de Análises Clínicas da Faculdade Evangélica de Ceres (Goiás).

A GJ foi analisada pelo método enzimático colorimétrico em aparelho Labmax Plenno® (analisador bioquímico automático), e considerado como adequado o valor de referência ≤ 99 mg/dL (AMERICAN DIABETES ASSOCIATION, 2019a).

O CT, HDL-c e TG foram obtidos pelo método enzimático colorimétrico, também no aparelho Labmax Plenno®, com o LDL-c e o não HDL-c calculados a partir da subtração do colesterol total pelo HDL-c e VLDL-c, e pela diferença entre o CT e o HDL-c, respectivamente (FALUDI et al., 2017). A partir do CT, LDL-c, TG e HDL-c calculou-se as razões CT/HDL-c, LDL-c/HDL-c e TG/HDL-c. Os valores de referência considerados adequados foram: < 170 mg/dL para o CT, > 45 mg/dL para o HDL-c, < 110 mg/dL para o LDL-c, e < 75 mg/dL e < 90 mg/dL para o TG entre pessoas de 0-9 anos e 10-19 anos, respectivamente (FALUDI et al., 2017).

A 25(OH)D plasmática foi avaliada pelo método de cromatografia líquida de alta eficiência com detector de arranjo de diodos (CLAE-DAD). Foi utilizado um cromatógrafo líquido de alta eficiência Accela 600, controlado pelo programa ChromQuest 5.0 (Thermo Scientific®, San Jose, USA) e seguindo a metodologia de Kich e colaboradores (2012). Valores séricos de 25(OH)D < 50 nmol/L foram considerados deficientes, 52,5-72,5 nmol/L como insuficientes e ≥ 75 nmol/L como suficientes (HOLICK et al., 2011).

4.7.6 Consumo alimentar

A avaliação do consumo de energia e nutrientes foi realizado por meio do recordatório de 24 horas (Apêndice 5). No total, foram aplicados 12 recordatórios de 24 horas com cada participante, sendo três em cada um dos períodos (T_1, T_2, T_3 e T_4). O primeiro recordatório de cada período foi aplicado pessoalmente, e os demais via telefone, todos com a presença de um responsável pela criança. Os três recordatórios de 24 horas foram obtidos em dias não consecutivos, considerando um dia de final de semana.

A média da ingestão energética, de macronutrientes (carboidrato, proteína e lipídeo), colesterol, fibra, sódio, vitamina D, cálcio e ferro foi calculada no programa Diet Pro®. Estes dados foram utilizados para acompanhar e avaliar possíveis alterações no comportamento alimentar durante o período de intervenção.

Para a avaliação do consumo dietético de vitamina D considerou-se a ingestão diária recomendada de 600 UI/dia (INSTITUTE OF MEDICINE, 2011).

4.8 ANÁLISE ESTATÍSTICA

Todos os dados foram tabulados em dupla entrada, por meio do programa Microsoft Excel® versão 15.26.

Os dados da linha de base das crianças selecionadas para o estudo transversal (n=88) foram avaliados quanto a normalidade de distribuição por

meio do teste Shapiro-Wilk. As variáveis contínuas foram apresentadas em média e desvio-padrão e as variáveis categóricas em frequência relativa. Para algumas análises estatísticas, a amostra foi estratificada em dois grupos segundo os valores séricos de vitamina D: 75-99 e ≥ 100 nmol/L. A comparação da frequência de sexo, raça auto-referida e prática de atividade física, de acordo com os níveis séricos de 25(OH)D, foi realizada pelo Qui-quadrado de Pearson. A comparação da idade, variáveis antropométricas, composição corporal e perfil metabólico, também segundo os níveis séricos de 25(OH)D, foi feita a partir dos testes de t-Student para amostras independentes, com as variáveis paramétricas, e Mann-Whitney, com as não paramétricas. A análise de regressão linear simples foi realizada para avaliar o efeito da concentração de vitamina D sobre a composição corporal e o perfi metabólico, ajustado pelo sexo. Foi utilizado o software *SPSS* (*Statistical Package Science Social*), versão 21.0, considerando-se $p < 0,05$ com todas as análises corrigidas pelo método de Bonferroni para o controle de múltiplas comparações.

Após a exclusão dos valores discrepantes dos dados das crianças incluídas no ensaio clínico (n=62), a normalidade das variáveis foi realizada pelo teste de Lilliefors. As variáveis categóricas foram apresentadas em frequência relativa e as contínuas em média e desvio-padrão. O efeito de *carryover* foi analisado conforme Rosner (2011). Para eliminação do efeito de *carryover* significante, foi realizada análise de variância (ANOVA fatorial) com os deltas ajustados pelos valores iniciais. O teste de comparação das médias foi ajustado pela idade e realizado por meio da ANOVA fatorial e pelo teste de diferenciação de Tukey. Para isto, foi realizada transformação logarítmica das variáveis não paramétricas. Foram utilizados os programas R e RStudio, e adotado nível de significância de 5%.

5 PUBLICAÇÕES

Artigo 1 – Vitamin D is not associated with body composition and metabolic profile among Brazilian children with 25-hydroxyvitamin D ≥ 75 nmol/L: a cross-sectional study

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Revista: Nutrition, Metabolism & Cardiovascular Diseases

Fator de impacto: 3.700

Situação: Aprovado

Artigo 2 – Vitamin D supplementation reduces serum lipids of children with hypertriglyceridemia: a randomized, triple-masked, placebo-controlled crossover trial

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Situação: Em revisão

5.1 ARTIGO 1

Vitamin D is not associated with body composition and metabolic profile among Brazilian children with 25-hydroxyvitamin D ≥ 75 nmol/L: a cross-sectional study

Abstract

Background and aims: The association of vitamin D with cardiovascular disease risk factors among children remains inconclusive, and there is a lack of studies that evaluate children with optimal serum 25-hydroxyvitamin D [25(OH)D]. Thus, this study aimed to analyze the relationship between serum 25(OH)D and body composition and metabolic profile among Brazilian children with sufficient serum 25(OH)D.

Methods and results: A cross-sectional study was conducted with 88 Brazilian children aged 4-11 years. Self-reported race, physical activity, anthropometry (body mass and height), body composition (waist circumference, body fat percentage, fat free mass, triceps and subscapular skinfolds), biochemical profile [lipid fractions, fasting glucose and 25(OH)D] and blood pressure data were collected. No difference was found in sex, self-reported race, physical activity, age, anthropometry, body composition, biochemical parameters and blood pressure between children with 25(OH)D 75-99 and ≥ 100 nmol/L. In addition, there was no association between serum vitamin D and body composition and metabolic profile.

Conclusions: Serum 25(OH)D was not associated with body composition and metabolic profile among Brazilian children with sufficient serum 25(OH)D.

Further studies among children with serum levels ≥ 75 nmol/L are needed to confirm this finding.

Keywords: Vitamin D; 25(OH)D; Triglycerides; Lipoproteins; Children

Introduction

Vitamin D is a fat-soluble metabolite important for bone health,[1] and it also has extraskeletal benefits, such as the improvement of serum lipids.[2] Among the biological markers that characterize the lipid profile are total cholesterol (TC) and triglycerides (TG), and their increased values are related to a greater risk to develop cardiovascular disease (CVD).[3,4]

Actions that prevent CVD should be initiated in childhood,[5] and adequate serum vitamin D can contribute to this purpose.[6]

The recommendation to maintain serum 25(OH)D ≥ 75 nmol/L was based on bone health,[7] and this cut-off point may vary according to the health outcome of interest, such as cardiovascular, but there is no global recommendation on this matter so far. The Endocrine Society Clinical Practice Guidelines indicate vitamin D serum levels between 100-150 nmol/L, for all age groups, to ensure support to physiological demands.[7]

In relation to childhood, serum concentration above 75 nmol/L could be beneficial to health, since the growth and development at this life stage may require different values from adults, which was the population evaluated to establish this recommendation.[8]

Regarding the relationship between vitamin D and serum lipids, studies were performed mostly with deficient (< 50 nmol/L) or insufficient (52.5-72.5

nmol/L) children,[9,10] and studies among adequate (≥ 75 nmol/L) individuals are lacking. Meta-analysis have already demonstrated a positive[11] and negative[12] effect of serum vitamin D on lipid profile among children, remaining inconclusive this association.

Other risk factors related to the development of CVD, such as obesity and hypertension, were inversely associated with serum vitamin D in studies conducted with children.[13,14]

Thus, our aim was to analyze the relationship between serum 25(OH)D and body composition and metabolic profile among Brazilian children with sufficient serum 25(OH)D.

Methods

Study design, sample size and ethical aspects

This is a cross-sectional study, carried out in 2018 in the Midwest region of Brazil, and which is part of a larger project entitled “Metabolic syndrome: metabolic, oxidative and inflammatory responses of physical exercise and nutritional programs in 4 to 11-year-old school children from Santo Antônio de Goiás, Brazil”.

Inclusion criteria were: age between 4 and 11 years and sufficient serum 25(OH)D (≥ 75 nmol/L).[7] Children with some physical or cognitive disability that would compromise data collection were excluded.

In total, 101 children agreed to participate, but 13 were excluded for having insufficient serum vitamin D (52,5-72,5 nmol/L), resulting in a final number of 88 subjects (39 girls and 49 boys). For some statistical analysis, the

sample was stratified into two groups, according to 25(OH)D levels: 75-99 and ≥ 100 nmol/L.

The sample size of children included in the study had a power of 0.80, α = 0.05, β = 0.20 and effect size of 0.54, which means that the sample presented a medium effect size[15], performed in G*Power 3.1.

Children and parents signed the Term of Free and Informed Assent and the Term of Free and Informed Consent, respectively. This research was approved by the Research Ethics Committee of the Federal University of Goiás [protocol nº 1.970.935 and Certificate of Presentation for Ethical Appreciation (CAAE) nº 62297616.7.0000.5083].

Evaluation protocols

From a specific questionnaire, self-reported race and physical activity data were collected. The latter was evaluated using the Physical Activity Questionnaire for Older Children (PAQ-C) and classified as active when the practice of physical activity was at least 60 minutes/day or little active when the time was < 60 minutes/day.[16]

Regarding anthropometry and body composition, body mass was measured on an electronic scale (Seca®, model 813, Hamburg, Germany) and height on a portable stadiometer (Seca®, model 213, Hamburg, Germany). From these two variables, body mass index (BMI) (kg/m²) was obtained and classified as high when the BMI-for-age was > 85th percentile.[17]

Waist circumference (WC) (cm) was measured in duplicate at the midpoint between the lower portion of the last rib and the iliac crest[18] with an

inextensible anthropometric tape (Cescorf®, Porto Alegre, Brazil), which was classified as high if the WC was ≥ 75th percentile.[19]

Waist-to-height ratio (WHtR), calculated by dividing WC by height, was classified as high when the value obtained was > 0.50.[20]

Body fat (BF) percentage and fat free mass (FFM) (kg) were determined from the resistance and reactance measured by tetrapolar bioimpedance (Bioelectrical Impedance Analyzer, RJL Systems®, model Quantum II, Michigan, United States of America). The RJL Systems® online software was used for analysis. The BF % ≥ 85th percentile was classified as high.[21]

Triceps (TSF) and subscapular (SSF) skinfolds (mm) were measured in duplicate according to the International Society for the Advancement of Kinanthropometry (ISAK) protocol,[18] with a Lange® adipometer (Beta Technology Inc., Santa Cruz, United States of America).

Biochemical parameters and blood pressure were considered to assess the metabolic profile. Blood was drawn from the children fasting for 8-12 hours, and lipid profile (TC, HDL-c, LDL-c, non-HDL-c and TG), fasting glucose (FG) and 25(OH)D were determined. TC, HDL-c, TG and FG were evaluated by enzymatic colorimetric method using the Labmax® Plenno automatic analyzer. LDL-c and non-HDL-c were obtained from mathematical equation.[22] TC, LDL-c, TG and HDL-c were used to calculate TC/HDL-c, LDL-c/HDL-c and TG/HDL-c ratio. Serum 25(OH)D was measured by high performance liquid chromatography – diodearray detector (HPLC-DAD).

Reference values considered inadequate were: TC ≥ 170 mg/dL, HDL-c ≤ 45 mg/dL, LDL-c ≥ 110 mg/dL, TG ≥ 75 and ≥ 90 mg/dL for subjects aged 0-9 and 10-19 years, respectively, and FG > 99 mg/dL.[22,23]

Systolic (SBP) and diastolic (DBP) blood pressure (mmHg) were determined with the Omron HBP-1100 professional portable monitor (Omron®, Hoofddorp, The Netherlands), according to the Brazilian Society of Cardiology recommendation.[24] For the classification of SBP and DBP, values > 95th percentile were considered high.[25]

Statistical analysis

Double data entry was performed in Excel®, and analyzed using SPSS (Statistical Package Science Social) software 21.0. Normal distribution of the data was determined by Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables in relative frequency (%).

A comparison of the frequency of sex, self-reported race and physical activity, according to the vitamin D stratification, was performed by Pearson's Chi-square. Mean values of age, anthropometry, body composition and metabolic profile were compared by unpaired Student's t-test, with parametric variables, and Mann-Whitney test, with non-parametric variables. A simple linear regression analysis was performed to examine the effect of serum 25(OH)D on body composition and metabolic profile, adjusted for sex. P-value < 0.050 was considered significant, and all analysis were corrected by Bonferroni method to control for multiple comparisons.

Results

In relation to body composition, the frequency of inadequate BMI, WC, WHtR and BF (%) among the children evaluated (n = 88) was 43.18%, 35.23%, 22.73% and 86.36%, respectively. TC, TG and LDL-c were high in 37.5%, 61.36% and 25.0% of the children, respectively, and 28.41% presented low HDL-c. All children had adequate values of SBP, DBP and FG.

No difference was found in sex, self-reported race and physical activity between groups with 25(OH)D 75-99 and ≥ 100 nmol/L (P-value ≥ 0.017) (Table 1).

In relation to age, anthropometry, body composition, biochemical parameters and blood pressure, there was also no difference between groups (P-value ≥ 0.002) (Table 2).

There was no association between body composition and serum 25(OH)D of the children (P-value ≥ 0.007) (Table 3), and between metabolic profile and vitamin D (P-value ≥ 0.005) (Table 4).

Discussion

The findings of this study are relevant since they showed that serum vitamin D levels were not associated with body compositon and metabolic profile among children with sufficient 25(OH)D.

Studies identified an inverse[10,26-30] and no association[31-33] between serum vitamin D and lipid profile of children. Those that found lower mean lipoproteins ratio (TG/HDL-c and TC/HDL-c), TG, non-HDL-c and TC among

children with higher values of 25(OH)D ($p < 0.050$) stratified the sample with and without serum deficiency (< and ≥ 50 nmol/L, respectively).[10,26,27] Moreover, the investigations that showed an inverse and significant relationship between vitamin D and TG, TC and LDL-c ($p < 0.050$) included in the sample children with serum 25(OH)D deficiency (< 50 nmol/L) and insufficiency (52.5-72.5 nmol/L)[28-30], while the present study evaluated only children with sufficient 25(OH)D.

Birken et al.[34] identified that the increase of each 10 nmol/L in serum 25(OH)D of 1,961 Canadian children with mean 25(OH)D of 85,00±30,00 nmol/L led to a reduction of -2.34 mg/dL in TG ($p < 0.0001$), -0.89 mg/dL in non-HDL-c ($p = 0.0004$) and -1.08 mg/dL in TC ($p < 0.0001$), association not found among the 88 Brazilian children evaluated that had mean 25(OH)D of 100.57±15.32 nmol/L ($p \geq 0.005$).

Among the children assessed, no association was found between vitamin D and body composition ($p \geq 0.050$), but in a research with 2,680 Chinese children and adolescents an inverse relationship between vitamin D and BMI ($p = 0.048$) was observed.[35] Probably the difference in these findings was because Tang et al.[35] included in the sample children and adolescents with deficiency and inadequacy of serum 25(OH)D, and in the present study only children with sufficient vitamin D were evaluated.

An investigation with 378 Brazilian children found that vitamin D above 80 nmol/L was associated with 49% lower cardiometabolic risk prevalence,[36] cut-off point higher than the current recommendation to maintain serum levels above 75 nmol/L.[7] This finding contributes to demonstrate the importance of serum 25(OH)D above 80 nmol/L among children, but although the

participants of the present study had mean vitamin D higher than this value (100.57±15.32 nmol/L), most of them presented excess body fat, high TG and low physical activity practice, which demonstrates the need to monitor this population to modify their inappropriate lifestyle, such as sedentariness and inadequate food choices, and prevent the development of future health issues.[37,38]

The increase in vitamin D levels among children with sufficient serum 25(OH)D did not enhanced body composition and metabolic profile. Nevertheless, sun exposure, use of supplements and vitamin D food source intake should be encouraged for the maintenance of 25(OH)D levels among children with sufficient concentratiion, for cardiovascular health. However, randomized clinical trials are required to confirm this recommendation.

Since this is a cross-sectional study, the design makes it difficult to understand the causal relationship between serum vitamin D and anthropometric, body composition and metabolic variables, which is a limitation of this research, in addition to the non-assessment of children's sun exposure habit and perinatal history, as maternal serum 25(OH)D during pregnancy and lactation influence the concentration of this vitamin among children.[39,40]

The sample size might be considered a strength of this study, since all participants had sufficient serum 25(OH)D and more than 65% of the Brazilian children have vitamin D concentration below 75 nmol/L.[41]

Conclusions

In the present study, 25(OH)D levels in children with serum concentration ≥ 75 nmol/L were not associated with body composition and metabolic profile.

More researches with children with sufficient serum vitamin D are necessary, including randomized clinical trials, besides the establishment of 25(OH)D reference range specific for pediatric age for a more assertive clinical practice among this population.

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Table 1. Characterization of sex, self-reported race and physical activity of the children, according to serum 25(OH)D.

	Serum 25(OH)D (nmol/L)	
	75-99 (n=40)	≥ 100 (n=48)
Sex		
Male	21(52.5)	28(58.3)
Female	19(47.5)	20(41.7)
Self-reported race		
White	11(27.5)	23(47.9)
Black	1(2.5)	1(2.1)
Brown	28(70.0)	24(50.0)
Physical activity		
Active	13(32.5)	10(20.8)
Little active	27(67.5)	38(79.2)

Data are presented in n(%).

No difference was found between groups (Bonferroni-corrected P-value = 0.017).

Table 2. Comparison of age, anthropometry, body composition and metabolic profile of the children, according to serum 25(OH)D.

	All included children (n=88)	Serum 25(OH)D (nmol/L)	
		75-99 (n=40)	≥ 100 (n=48)
Age (years)	6.73(1.73)	6.82(1.72)	6.64(1.76)
Height (m)	1.25(0.11)	1.26(0.13)	1.25(0.10)
Body mass (kg)	28.78(9.84)	29.32(10.71)	28.33(9.15)
BMI (kg/m^2)	17.88(3.54)	18.05(3.72)	17.74(3.42)
WC (cm)	59.64(8.98)	60.20(9.74)	59.18(8.38)
WHtR	0.48(0.05)	0.48(0.06)	0.47(0.05)
BF (%)	30.92(10.18)	31.40(10.56)	30.52(9.95)
FFM (kg)	19.24(4.44)	19.53(4.94)	19.00(4.02)
TSF (mm)	13.47(6.87)	13.93(7.61)	13.08(6.23)
SSF (mm)	9.70(6.92)	10.16(7.38)	9.32(6.56)
TC (mg/dL)	160.76(28.98)	165.68(31.84)	156.67(25.99)
HDL-c (mg/dL)	52.52(12.19)	51.00(12.41)	53.79(11.98)
TG (mg/dL)	90.60(32.68)	98.70(36.05)	83.85(28.20)
LDL-c (mg/dL)	90.78(29.26)	95.60(31.54)	86.75(26.88)
Non-HDL-c (mg/dL)	108.20(31.28)	114.74(34.18)	102.88(27.96)
TC/HDL-c	3.24(1.02)	3.45(1.08)	3.07(0.94)
TG/HDL-c	1.87(0.96)	2.12(1.12)	1.67(0.77)
LDL-c/HDL-c	1.88(0.89)	2.03(0.93)	1.75(0.84)
FG (mg/dL)	79.53(7.87)	78.85(7.34)	80.10(8.32)
25(OH)D (nmol/L)	100.58(15.32)	87.62(6.78)	111.35(11.62)

SBP (mmHg)	92.27(11.90)	93.30(11.95)	91.42(11.92)
DBP (mmHg)	58.37(9.05)	60.22(9.38)	56.82(8.55)

Data are presented in mean (SD).

BMI: body mass index; WC: waist circumference; WHtR: waist-to-height ratio; BF: body fat; FFM: fat free mass; TSF: triceps skinfold; SSF: subscapular skinfold; TC: total cholesterol; TG: triglycerides; FG: fasting glucose; 25(OH)D: 25-hydroxyvitamin D; SBP: systolic blood pressure; DBP: diastolic blood pressure.

No difference was found between groups with serum 25(OH)D 75-99 and ≥ 100 nmol/L (Bonferroni-corrected P-value = 0.002).

Table 3. Association between body composition and serum 25(OH)D of the children (n=88).

Dependent variables	Model 1				Model 2			
	Unstandardized coefficient		Standardized coefficient	$R^{2\,a}$	Unstandardized Coefficient		Standardized coefficient	$R^{2\,a}$
	B	95% CI	ß		B	95% CI	ß	
BMI (kg/m^2)	-0.026	-0.080, 0.029	-0.102	0.010	-0.026	-0082, 0.029	-0.105	0.012
WC (cm)	-0.058	-0.195, 0.078	-0.094	0.009	-0.065	-0.202, 0.071	-0.105	0.024
WHtR	0.000	-0.001, 0.000	-0.125	0.016	-0.001	-0.001, 0.000	-0.137	0.034
BF (%)	-0.080	-0.239, 0.078	-0.110	0.012	-0.076	-0.236, 0.084	-0.104	0.018
FFM (kg)	-0.016	-0.084, 0.052	-0.052	0.003	-0.017	-0.085, 0.051	-0.055	0.004
TSF (mm)	-0.078	-0.184, 0.028	-0.160	0.026	-0.078	-0.185, 0.029	-0.160	0.026
SSF (mm)	-0.067	-0.172, 0.037	-0.141	0.020	-0.068	-0.173, 0.038	-0.141	0.020

Model 1: unadjusted model; Model 2: adjusted for sex.

95% CI: 95% confidence interval; BMI: body mass index; WC: waist circumference; WHtR: waist-to-height ratio; BF: body fat; FFM: fat free mass; TSF: triceps skinfold; SSF: subscapular skinfold.

[a] Determination coefficient.

None of the analysis was statistically significant (Bonferroni-corrected P-value = 0.007).

Table 4. Association between metabolic profile and serum 25(OH)D of the children (n=88).

Dependent variables	Model 1				Model 2			
	Unstandardized coefficient		Standardized coefficient	$R^{2\,a}$	Unstandardized coefficient		Standardized coefficient	$R^{2\,a}$
	B	95% CI	ß		B	95% CI	ß	
TC (mg/dL)	-0.319	-0.773, 0.135	-0.153	0.023	-0.317	-0.775, 0.142	-0.151	0.023
HDL-c (mg/dL)	0.185	-0.003, 0.373	0.211	0.045	0.184	-0.006, 0.375	0.210	0.045
TG (mg/dL)	-0.516	-0.997, -0.034	-0.229	0.052	-0.516	-1.002, -0.030	-0.229	0.053
LDL-c (mg/dL)	-0.444	-0.894, 0.006	-0.212	0.045	-0.444	-0.899, 0.010	-0.212	0.045
TC/HDL-c	-0.019	-0.034, -0,003	-0.257	0.066	-0.019	-0.034, -0,003	-0.255	0.067
TG/HDL-c	-0.018	-0.032, -0.003	-0.259	0.067	-0.018	-0.032, -0.003	-0.257	0.067
LDL-c/HDL-c	-0.016	-0.029, -0.002	-0.248	0.061	-0.016	-0.029, -0.002	-0.247	0.061
FG (mg/dL)	0.001	-0.117, 0.118	0.002	0.000	-0.001	-0.120, 0.117	-0.002	0.002
SBP (mmHg)	-0.043	-0.230, 0.143	-0.051	0.003	-0.048	-0.236, 0.141	-0.056	0.006

DBP (mmHg)	-0.052	-0.196, 0.092	-0.079	0.006	-0.060	-0.204, 0.084	-0.092	0.027

Model 1: unadjusted model; Model 2: adjusted for sex.

95% CI: 95% confidence interval; TC: total cholesterol; TG: triglycerides; FG: fasting glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure.

[a] Determination coefficient.

None of the analysis was statistically significant (Bonferroni-corrected P-value = 0.005).

5.2 ARTIGO 2

Vitamin D supplementation reduces serum lipids of children with hypertriglyceridemia: a randomized, triple-masked, placebo-controlled crossover trial

Abstract

Objective: To evaluate the effect of cholecalciferol supplementation on body composition and metabolic profile of children with hypertriglyceridemia.

Material and Methods: This is a randomized, triple-masked, placebo-controlled crossover trial with 44 Brazilian children with hypertriglyceridemia, aged 4-11 years. The intervention lasted 34 weeks, with two periods of 12 weeks each separated by a 10-week washout. The two groups, supplemented and placebo, received 5 drops of cholecalciferol (equivalent to 1000 International Units/day) and 5 drops of sunflower oil, respectively, daily for 12 weeks. Sociodemographic, economic, sunscreen use, percentage of body surface area daily exposed to the sun, physical activity, anthropometry (body mass and height), body composition (waist circumference, body fat percentage, fat free mass, triceps and subscapular skinfolds), biochemical profile (25-hydroxyvitamin D, fasting glucose and lipid fractions), blood pressure and food intake data were collected.

Results: There was a reduction in serum total cholesterol (TC), LDL-c, non HDL-c, TC/HDL-c and LDL-c/HDL-c ratio in the supplemented group, when compared to the placebo group ($p < 0.05$).

Conclusions: Cholecalciferol supplementation was able to improve the lipid profile of children with hypertriglyceridemia, without altering body composition.

Keywords: Vitamin D; Triglycerides; Lipoproteins; Children; Clinical trial.

Introduction

Hypertriglyceridemia is a condition resulting from an inadequate lifestyle, such as poor diet quality and sedentary behavior [1]. When installed in childhood, there is a greater risk to develop cardiovascular disease (CVD) later in life [2]. Thereby, nutritional interventions need to be performed to lower the risk of morbidity and mortality during adulthood [3].

Vitamin D is one of the nutrients that influence serum triglycerides (TG), and studies have shown its role in reducing the concentration of this lipid fraction, in addition to other biomarkers such as total cholesterol (TC) and non HDL-cholesterol [4,5].

Despite its importance for health, only 10% of daily vitamin D requirements are obtained through diet, being obtained mostly by endogenous production from cutaneous exposure to ultraviolet B radiation [6]. However, considering some restrictions to prevent the development of skin cancer and behaviors that reduce outdoor activities with sun exposure, vitamin D supplementation is an alternative for increasing serum levels [6,7].

Regarding its supplementation, studies that evaluate the benefits in children with hypertriglyceridemia and without serum deficiency of this vitamin are lacking. Therefore, our aim was to evaluate the effect of cholecalciferol

supplementation on body composition and metabolic profile of children with hypertriglyceridemia.

Material and Methods

Study design and ethical statement

This is a 34-week, randomized, triple-masked, placebo-controlled crossover trial, involving children aged 4-11 years from a Brazilian public school, located in the Midwest region of the country. Data collection took place September 2017 thru December 2018, the children essessed for eligibility and their parents signed the Term of Free and Informed Assent and the Term of Free and Informed Consent, respectively. This study was approved by the Research Ethics Committee of the Federal University of Goiás (protocol nº 1.970.935 and Certificate of Presentation for Ethical Appreciation nº 62297616.7.0000.5083) and registered in the Brazilian Registry of Clinical Trial (ReBEC) [Universal Trial Number (UTN) U1111-1214-5845].

The assay was stratified in two 12-week phases, separated by a 10-week washout, whose period was equivalent to 5 times the 2-week plasma half-life of 25-hydroxyvitamin D [25(OH)D], established by the US Food and Drug Administration guidelines [8,9].

The supplemented (SG) and placebo (PG) group received, daily for 12 weeks, 5 drops of cholecalciferol in sunflower oil vehicle, equivalent to 1000 International Units (IU)/day, and 5 drops of sunflower oil, respectively. In order to better control the cholecalciferol intake, the supplement bottles were

delivered every 4 weeks, all parents were instructed to give the supplement to the children after lunch, filling out a spreadsheet with daily administration schedule, and all bottles lost or broken were immediately replaced.

The 1000 IU/day were established as a minimum daily dose required to increase serum 25(OH)D above 75 nmol/L, being a safe amount to maintain adequate plasma levels [10].

Food intake, blood pressure, body composition and biochemical parameters data collection occured at the beginning and end of each phase (Figure 1).

During the intervention period, parents were advised not to modify children's eating habits, physical activity and usual methods of sun protection and exposure.

Selection criteria, population and sample size

The inclusion criteria were: age between 4 and 11 years and have hypertriglyceridemia (TG ≥ 75 mg/dL and ≥ 90 mg/dL among children aged 0-9 years and ≥ 10 years, respectively) [11]. Children with chronic disease (hypertension, diabetes mellitus, kidney, liver, cardiovascular or autoimmune disease); physical or cognitive disability; in nutritional treatment; using any medication that influenced body composition, blood pressure, serum lipid or blood glucose; or on treatment with cholecalciferol were excluded. Regarding inclusion criteria, for evaluation of hypertriglyceridemia diagnosis, all children assessed for eligibility performed blood collection for analysis of serum TG.

Were invited to participate in the study 378 children, which represented the amount of children aged 4-11 years enrolled in the public school. The parents of 252 children attended the meeting for the presentation of the research's methodological procedures, and 101 signed the Term of Free and Informed Consent.

In total, 101 children were assessed for eligibility and 62 were included in the study for presenting hypertriglyceridemia. During the follow-up, 5 children moved residence and 8 declined to participate, so 49 concluded both arms of the study. However, were excluded from analysis who took less than 80.0% of the supplement, resulting in a final number of 44 subjects (Figure 2). Stratified randomization was performed aiming to eliminate potential biases in the distribuition of variables that could configure confusion fator between SG and PG [sex, age, body mass, height, 25(OH)D and serum lipid].

For sample size calculation, performed in G*Power 3.1, were considered serum TG of children supplemented with cholecalciferol in the study by Nader et al. [12]. Considering paired Student's t-test and type of power analysis "a priori: compute required sample size - given α, power and effect size", would be required a total of 14 subjects to achieve the power of 0.80 and effect size of 0.46. Nevertheless, 62 children were randomized and 44 were included from analysis, which represented a loss of 29.0% and a sample with effect size of 0.26 and power of 0.80.

Evaluation protocols

Self-reported race, family income, family members living together and sunscreen use data were collected from a specific questionnaire, percentage of body surface area daily exposed to the sun was evaluated according to Yin's publication [13], and the practice of physical activity was assessed through the application of the Physical Activity Questionnaire for Older Children (PAQ-C) [14].

Body mass was measured on an electronic scale (Seca®, model 813, Hamburg, Germany) and height on a portable stadiometer (Seca®, model 213, Hamburg, Germany), obtaining the body mass index (BMI) (kg/m^2). Body fat (BF) percentage and fat free mass (FFM) were determined by tetrapolar bioimpedance (Bioelectrical Impedance Analyzer, RJL Systems®, model Quantum II, Michigan, United States of America). Waist circumference (WC) was measured with an inextensible anthropometric tape (Cescorf®, Porto Alegre, Brazil), at the midpoint between the lower portion of the last rib and the iliac crest [15]. Waist-to-height ratio (WHtR) was calculated by dividing WC by height [16]. Triceps (TSF) and subscapular (SSF) skinfolds were measured with a Lange® adipometer (Beta Technology Inc., Santa Cruz, United States of America), according to the International Society for the Advancement of Kinanthropometry (ISAK) recommendations [15].

Metabolic profile was characterized from biochemical parameters and blood pressure. Blood collection was performed with children fasting for 8-12 hours. Serum 25(OH)D was evaluated by high performance liquid chromatography – diodearray detector (HPLC-DAD), and values < 50 nmol/L

were considered deficient, 52,5-72,5 nmol/L insufficient and ≥ 75 nmol/L sufficient [6]. Fasting glucose (FG), TC, HDL-c and TG were determined by enzymatic colorimetric method using the Labmax® Plenno automatic analyzer, with LDL-c and non HDL-c calculated by mathematical equation [11]. TC, LDL-c, TG and HDL-c were used to obtain TC/HDL-c, LDL-c/HDL-c and TG/HDL-c ratio.

Systolic (SBP) and diastolic (DBP) blood pressure were measured with the Omron HBP-1100 professional portable monitor (Omron®, Hoofddorp, The Netherlands), according to the Brazilian Society of Cardiology protocol [17].

Food intake evaluation was assessed through the 24-hour recall. In total, twelve 24-hour recalls were applied, two on a work day and the third on a weekend day, in each of the four periods (T_1, T_2, T_3 and T_4). Average intake of energy, carbohydrate, protein, lipid, cholesterol, fiber, sodium, vitamin D, calcium and iron were calculated in Diet Pro® software. For the evaluation of vitamin D intake, at baseline, was considered the Recommended Dietary Allowance (RDA) of 600 IU/day [18].

Statistical Analysis

Double data entry was performed, and software R 3.5.2 and RStudio 1.1.463 were used for all statistical analysis. Discrepant values were excluded and the analysis of normality of the variables was performed by the Lilliefors test. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables in relative frequency (%).

The carryover effect was analysed as explained by Rosner [19]. To eliminate significant carryover effect, analysis of variance (factorial ANOVA) was performed with the deltas adjusted by initial values. Mean tests were performed by factorial ANOVA adjusted by age, and Tukey test for post-hoc comparisons. Non-parametric variables were log-transformed. $P < 0.05$ was considered significant.

Results

At baseline, 18.18% (n=8) were insufficient and 81.82% (n=36) were sufficient in serum 25(OH)D, and the daily vitamin D dietary intake of the 44 children was 3,96±7,27 µg (158,4 IU), considered below the recommendation.

There was no difference in energy and nutrients intake between SG and PG during the intervention, identified by factorial ANOVA ($p \geq 0.05$).

SG and PG presented, at baseline, age of 7.43±1.78 and 7.06±1.80 years, and after 90 days 7.66±1.79 and 7.91±1.71 years, respectively, with difference in initial and final age between groups ($p = 0.049$ and $p < 0.001$, respectively).

No difference was found in sex, age, body composition, 25(OH)D, serum lipids and blood pressure between the subjects who concluded the study and dropped out of the study ($p \geq 0.05$) (Table 1).

Most children were brown race (54.5%), had monthly family income of 1-2 minimum wages (56.8%), lived with 4-5 relatives (59.1%), were little active (90.9%) and used sunscreen only at the pool, beach or river (68.2%). In

addition, they used to expose almost half of their bodies to the sun daily (45.50±8.5%) (Table 2).

At the end of the intervention, GS and PG increased height, body mass, FFM, WC, 25(OH)D and SBP ($p < 0.05$) (Tables 3 and 4). PG presented higher values of body mass when compared to SG ($p = 0.048$) (Table 3). Serum TC, LDL-c, non HDL-c, TC/HDL-c and LDL-c/HDL-c ratio decreased and 25(OH)D increased in SG when compared to PG ($p < 0.05$) (Table 4).

Discussion

Several clinical trials have already evaluated the effect of vitamin D supplementation on body composition and metabolic profile in humans, but the present study stands out by investigating this effect on children with hypertriglyceridemia and without serum 25(OH)D deficiency (< 50 nmol/L) [6].

The main finding of this study was that 1000 IU/day of cholecalciferol supplementation, for 90 days, reduced serum TC, LDL-c, non HDL-c, TC/HDL-c and LDL-c/HDL-c ratio, when compared to PG.

The effect of vitamin D supplementation on the reduction of TC and LDL-c is well established in the literature [20], including among children [5,21].

There is a direct relationship between TC, LDL-c and non HDL-c with the risk of developing CVD [22,23]. Regarding non HDL-c, it seems to be a better marker for CVD when compared to LDL-c [24], and the increase of each 10 nmol/L in serum 25(OH)D is associated to a reduction of -0,89 mg/dL in non HDL-c [25].

TC/HDL-c and LDL-c/HDL-c ratio are also directly associated to a higher CVD risk, and present inverse relationship with serum 25(OH)D [26,27]. Moreover, these lipoprotein ratio seem to be more related to the development of CVD when compared to other lipid fractions isolated [28,29], and individuals with LDL-c/HDL-c and TC/HDL-c ratio ≤ 2.0 and ≤ 3.5, respectively, appear to be risk-free from CVD [30-32]. Considering this recommendation, it was observed that in the present study the mean of these two lipoproteins ratio in the SG were reduced to adequate values after supplementation ($p = 0.035$ and 0.036, respectively). In relation to TC and LDL-c, although SG and PG had initiated the study with adequate means (< 170 mg/dL and < 110 mg/dL, respectively) [11], vitamin D supplementation reduced these two biochemical parameters, showing to be an alternative to prevent the increase of these markers.

Possible mechanisms by which vitamin D may exert an influence on lipid metabolism are the inhibition of expression of enzyme 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGR), with a consequent decrease in cholesterol synthesis [33], and indirectly by increasing calcium absorption which promotes a decrease in TC by converting them into bile acids [34].

The children in the present study had a vitamin D dietary intake below recommendation, which is commonly found in all age groups in populations such as the Brazilian, European and North American [35-37], and the existence of few food sources is one of the factors that contributes to this reality [38].

Despite of cholecalciferol supplementation did not reduce serum TG among children with hypertriglyceridemia, it was able to decrease other lipid

fractions, which demonstrates its role in the prevention of dyslipidemia and premature death due to CVD [39]. In addition, alternatives to drug therapy for improving lipid profile, such as vitamin D supplementation, may be beneficial to health, since statins, a class of medicine most used for this purpose, can have an adverse effects such as a decline in absorption of vitamin D which is important for a healthy childhood development [39-41].

Serum 25(OH)D, after 90 days, was higher in SG when compared to PG ($p < 0.001$), but the last group also showed an increase of this biomarker in relation to baseline ($p = 0.001$). This fact possibly occured due to endogenous synthesis of vitamin D through sunlight exposure [42], since there was no change in food intake during the intervention ($p \geq 0.05$).

Regarding anthropometry, there was an increase in body mass in PG when compared to SG, but not in other parameters such as BMI, WC, WHtR, BF (%), TSF and SSF, then cholecalciferol supplementation did not alter children's body composition. Besides that, when compared to baseline, both groups increased height, body mass, FFM, WC and SBP, which occured because the participants are children and, at this life stage, the increment of these variables tracks chronological age [43-45].

The non-evaluation of biochemical parameters related to the matabolism of 25(OH)D, such as calcium and parathyroid hormone, was a limitation of this study. However, the study design, the sample size and the length of intervention might be considered strengths of this study.

Conclusions

This clinical trial investigated the effect of increasing serum 25(OH)D on children with hypertriglyceridemia and without vitamin D deficiency, identifying that the supplementation of 1000 IU/day for 90 days was able to reduce serum TC, LDL-c, non HDL-c, TC/HDL-c and LDL-c/HDL-c ratio, without changing body composition.

Cholecalciferol supplementation was beneficial for cardiovascular health of children even with sufficient 25(OH)D (≥ 75 nmol/L).

These findings demonstrate the importance of the development of researchs that evaluate the cholecalciferol supplementation effects on children without 25(OH)D deficiency, seeking to reach higher values within the reference range for the attainment of extraskeletal benefits, and even propose cut-off points for the prevention of CVD.

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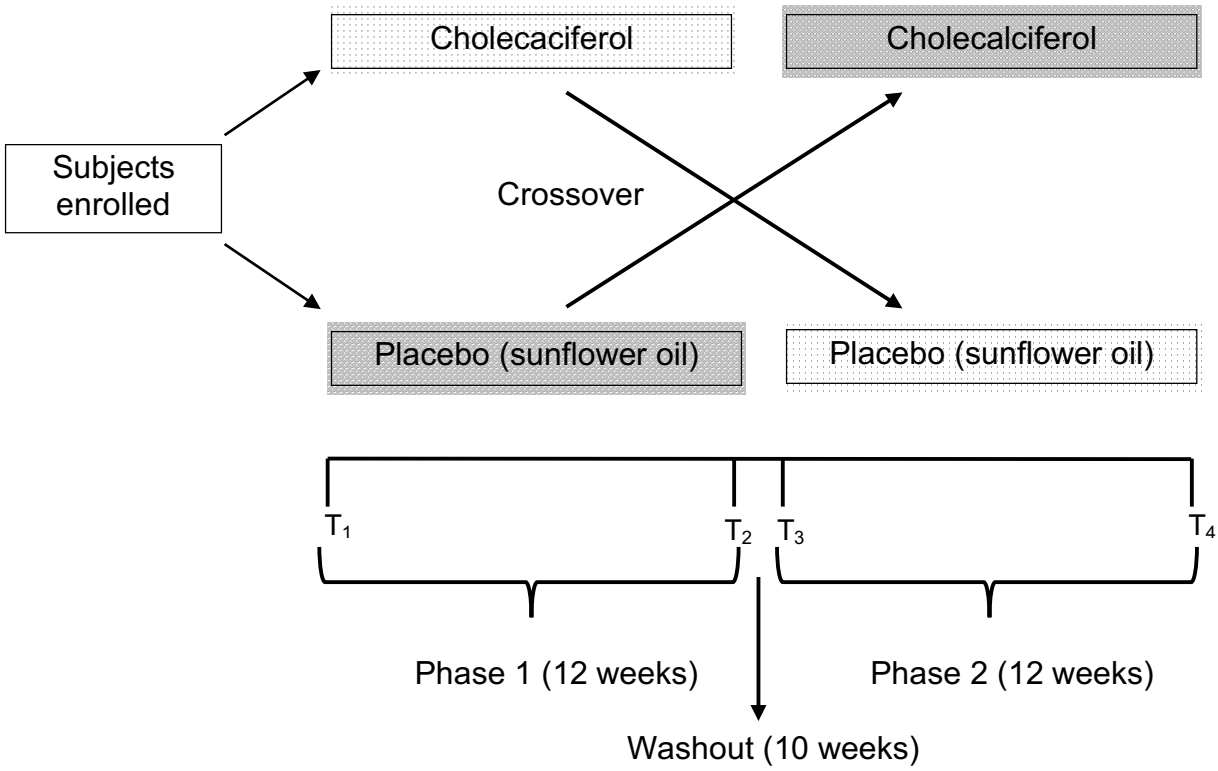
Figure 1. Study design.



T_1, T_2, T_3 and T_4: Food intake, blood pressure, body composition and biochemical profile evaluation.

Figure 2. Flow diagram throughout the study.

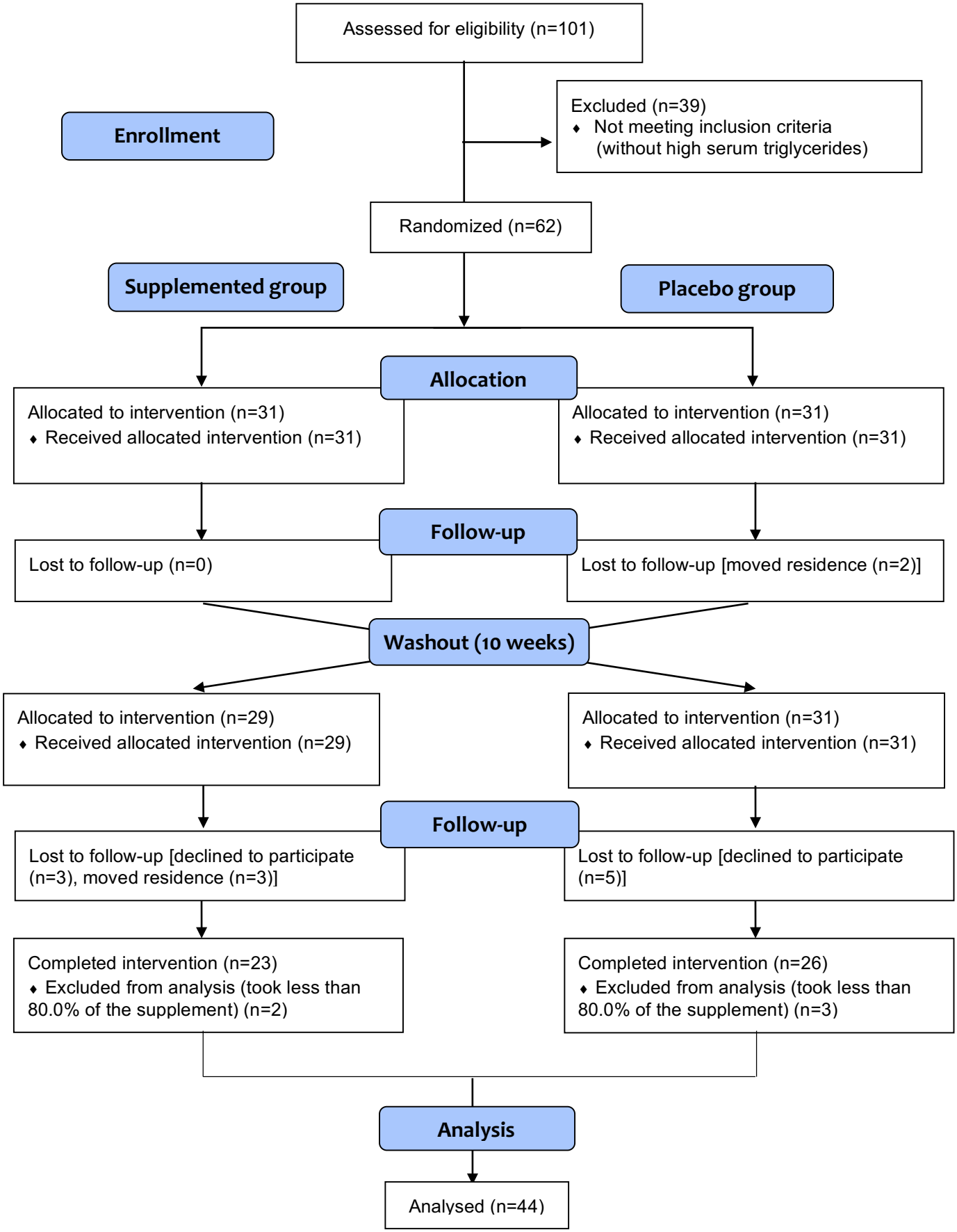


Table 1. Comparison of baseline characteristics of children who concluded the study and dropped out of the study.

Characteristics	Concluded study (n=44)	Dropped out of study (n=18)	P value
Sex			0.093[1]
Male	19(43.2)	12(66.7)	
Female	25(56.8)	6(33.3)	
Age (years)	6.86±1.75	7.39±1.50	0.268[2]
BMI (kg/m^2)	18.89±4.37	19.17±3.87	0.693[3]
BF (%)	34.23±11.01	33.53±9.93	0.816[2]
WHtR	.49±.07	.49±.06	0.504[3]
25(OH)D (nmol/L)	38.50±7.93	36.22±8.28	0.197[3]
TC (mg/dL)	169.25±29.18	173.56±30.34	0.604[2]
LDL-c (mg/dL)	98.85±28.97	96.93±30.92	0.817[2]
TG (mg/dL)	115.43±40.99	106.06±27.42	0.515[3]
HDL-c (mg/dL)	48.14±12.59	51.39±6.18	0.302[2]
Non HDL-c (mg/dL)	121.11±30.16	117.17±33.66	0.653[2]
TC/HDL-c	3.75±1.14	3.42±.71	0.457[3]
LDL-c/HDL-c	2.23±.96	1.92±.68	0.344[3]
TG/HDL-c	2.66±1.46	2.08±.56	0.292[3]
SBP (mmHg)	95.00±11.24	91.67±10.43	0.284[2]
DBP (mmHg)	60.12±8.21	61.17±8.63	0.656[2]

Data are presented in n(%) or mean±SD.

BMI: body mass index; BF: body fat; WHtR: waist-to-height ratio; 25(OH)D: 25-hydroxyvitamin D; TC: total cholesterol; TG: triglycerides; SBP: systolic blood pressure; DBP: diastolic blood pressure.

[1]Pearson's Qui-square.

[2] Unpaired Student's t-test.

[3] Mann-Whitney test.

Table 2. Characterization of the children who concluded the study (n=44).

Variables		
Race	White	19(43.2)
	Black	1(2.3)
	Brown	24(54.5)
Family income	< 1MW	6(13.6)
	1-2 MW	25(56.8)
	> 2 MW	13(29.6)
Family members living together	2-3	11(25.0)
	4-5	26(59.1)
	6-7	7(15.9)
Physical activity	Active	4(9.1)
	Little active	40(90.9)
BSA (%)		45.50±8.51
Sunscreen use	Every day	7(15.9)
	Only at the pool/ beach/river	30(68.2)
	Never	7(15.9)

MW: minimum wage (1 MW = R$ 1045.00, which represents approximately USD 186.00); BSA (%): percentage of body surface area daily exposed to the sun.

Data are presented in n(%) or mean±SD.

Table 3. Children's anthropometric variables and body composition at baseline and after 90 days of treatment with cholecalciferol supplementation and placebo (n=44).

	SG				PG				
	Baseline	90 days	P value [a]	Delta	Baseline	90 days	P value [a]	Delta	P value [b]
Height	1.30(0.12)	1.33(0.11)	<0.001	0.03(0.02)	1.30(0.12)	1.33(0.11)	<0.001	0.03(0.02)	0.614
Body mass	32.79(11.70)	34.28(11.55)	0.005	1.49(1.75)	33.14(11.88)	34.92(11.93)	0.004	1.78(2.48)	0.048
BMI	19.03(4.43)	19.00(4.36)	0.868	-0.04(1.00)	19.12(4.89)	19.28(4.66)	0.468	0.15(1.38)	0.087
BF	33.75(11.68)	32.70(11.83)	0.258	-1.05(3.66)	34.36(12.17)	33.28(12.68)	0.782	-1.08(3.29)	0.131
FFM	20.82(5.56)	22.14(5.48)	<0.001	1.32(1.08)	20.64(5.00)	22.17(5.18)	<0.001	1.53(1.08)	0.730
WC	62.94(11.33)	65.19(12.11)	0.001	2.25(3.45)	62.87(11.25)	65.45(12.60)	0.003	2.58(3.24)	0.600
WHtR	0.48(0.07)	0.49(0.08)	0.454	0.004(0.03)	0.48(0.07)	0.49(0.08)	0.296	0.007(0.03)	0.830
TSF	16.63(7.80)	16.51(7.80)	0.614	-0.12(3.84)	16.63(7.87)	16.70(7.99)	0.204	0.07(3.12)	0.592
SSF	13.44(8.64)	14.57(10.17)	0.356	3.07(5.00)	14.03(9.62)	14.76(9.88)	0.474	2.67(5.11)	0.622

TSF+SSF	30.06(16.04)	31.08(17.32)	0.658	1.02(8.10)	30.66(17.08)	31.46(17.49)	0.281	0.80(6.77)	0.950

SG: supplemented group; PG: placebo group; Height: m; Body mass: kg; BMI: body mass index (kg/m^2); BF: body fat (%); FFM: fat free mass (kg); WC: waist circumference (cm); WHtR: wais-to-height ratio; TSF: triceps skinfold (mm); SSF: subscapular skinfold (mm).

Values are presented in mean(SD).

[a] Within group comparisons (factorial ANOVA adjusted by age).

[b] Between groups comparisons of delta values (factorial ANOVA adjusted by age).

Table 4. Children's metabolic profile at baseline and after 90 days of treatment with cholecalciferol supplementation and placebo (n=44).

	SG				PG				
	Baseline	90 days	P value [a]	Delta	Baseline	90 days	P value [a]	Delta	P value [b]
25(OH)D	87.38(18.35)	124.20(28.10)	<0.001	36.82(29.45)	89.02(20.85)	93.08(21.50)	0.001	4.02(13.40)	<0.001
FG	84.59(9.13)	82.50(9.15)	0.152	-2.09(12.22)	84.86(7.59)	83.52(6.98)	0.112	-1.34(8.98)	0.535
TC	165.57(27.99)	160.00(38.57)	0.053	-5.57(26.81)	167.75(26.82)	172.36(22.48)	0.839	4.61(18.56)	<0.001
LDL-c	96.42(26.41)	92.90(33.53)	0.098	-3.53(26.03)	98.86(24.66)	106.56(19.51)	0.560	7.70(15.47)	<0.001
TG	109.32(44.55)	97.23(41.58)	0.053	-12.09(34.15)	102.48(33.33)	101.36(30.76)	0.644	-1.11(37.10)	0.161
HDL-c	48.66(12.79)	48.16(10.44)	0.972	-0.50(8.44)	48.20(11.45)	46.27(9.53)	0.807	-1.93(11.68)	0.298
Non HDL-c	116.91(30.03)	111.84(36.09)	0.057	-5.07(27.79)	119.54(24.18)	126.09(21.46)	0.754	6.54(18.50)	<0.001
TC/HDL-c	3.64(1.15)	3.40(0.82)	0.036	-0.23(0.89)	3.62(0.82)	3.84(0.77)	0.653	0.22(0.89)	0.001
LDL-c/HDL-c	2.17(0.94)	1.99(0.72)	0.035	-0.18(0.78)	2.14(0.70)	2.39(0.66)	0.434	0.24(0.69)	<0.001

TG/HDL-c	2.51(1.55)	2.17(1.22)	0.062	-0.34(0.94)	2.32(1.21)	2.32(0.96)	0.734	-0.01(1.19)	0.237
SBP	95.83(9.49)	102.22(9.49)	0.002	6.39(9.76)	95.08(11.77)	103.24(9.55)	0.003	8.16(10.01)	0.501
DBP	60.76(7.82)	62.65(8.90)	0.334	1.89(9.80)	59.77(7.99)	62.27(8.07)	0.332	2.50(10.44)	0.422

SG: supplemented group; PG: placebo group; 25(OH)D: 25-hydroxyvitamin D (nmol/L); FG: fasting glucose (mg/dL); TC: total cholesterol (mg/dL); TG: triglycerides (mg/dL); SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg). LDL-c, HDL-c and non HDL-c: mg/dL.

Values are presented in mean(SD).

[a] Within group comparisons (factorial ANOVA adjusted by age).

[b] Between groups comparisons of delta values (factorial ANOVA adjusted by age).

6 CONSIDERAÇÕES FINAIS

O presente estudo demonstrou que concentrações séricas de vitamina D não se associou com a composição corporal e o perfil metabólico de crianças avaliadas com níveis de 25(OH)D ≥ 75 nmol/L, e que a suplementação de 1000 UI/dia de colecalciferol, por 90 dias, em crianças hipertrigliceridêmicas e sem deficiência desse marcador, foi capaz de reduzir as concentrações de CT, LDL-c, não HDL-c e das frações CT/HDL-c e LDL-c/HDL-c.

Diante disso, a suplementação de vitamina D pode ser benéfica não só para indivíduos com deficiência ou insuficiência sérica, mas também entre aqueles com concentrações consideradas suficientes, porém mais estudos são necessários para essa confirmação.

Os achados sobre a suplementação de colecalciferol em crianças sem deficiência desta vitamina configuram-se como um propulsor para o desenvolvimento de outras pesquisas que avaliem os benefícios que o aumento da vitamina D pode proporcionar ao organismo de indivíduos com fator de risco cardiovascular instalado. Isso poderia estimular os órgãos competentes a avaliarem possíveis novas recomendações dos níveis séricos de 25(OH)D para benefícios extra-ósseos, visto que a orientação de 75 nmol/L foi estabelecida visando a saúde óssea.

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ANEXOS

Anexo 1 – Parecer do Comitê de Ética

UFG - UNIVERSIDADE FEDERAL DE GOIÁS

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Síndrome metabólica: respostas metabólicas, oxidativas e inflamatórias de programas de exercício físico e nutricional em escolares de 4 a 11 anos de Santo Antônio de Goiás

Pesquisador: Maria Sebastiana Silva

Área Temática:

Versão: 4

CAAE: 62297616.7.0000.5083

Instituição Proponente: Universidade Federal de Goiás

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.970.935

Apresentação do Projeto:

Trata-se de um projeto guarda-chuva (com cinco subprojetos aninhados) que avaliará aspectos relacionados à síndrome metabólica em crianças. Para avaliar o efeito de programas de exercício físico e nutricional sobre as respostas metabólicas, oxidativas e inflamatórias em escolares de 4 a 11 anos de idade na cidade de Santo Antônio de Goiás, serão recrutadas crianças a partir da população de escolares na faixa etária descrita, do referido município (duas escolas de ensino básico que no ano de 2015 tinham matriculadas 780 crianças com idade entre 4 a 11 anos). As variáveis a serem analisadas serão: bioquímicas (glicemia de jejum e perfil lipídico), ntropométricas (circunferência da cintura) e sinais clínicos (aferição da pressão arterial) para diagnóstico da síndrome metabólica. Também serão avaliados o índice de massa corporal, a composição corporal por bioimpedância elétrica e por radiologia por densitometria por dupla emissão de raios-X, bem como concentrações séricas de proteína C-reativa (PCR), homocisteína e glutationa peroxidase, além da capacidade física (PROESP-BR) e cardiorrespiratória (teste de esforço cardiopulmonar – TECP). O protocolo é dividido em: 1) estudo transversal, que avaliará a prevalência da síndrome metabólica, a composição corporal e o processo inflamatório das crianças; 2) estudos caso-controle que estimarão a concentração de enzimas envolvidas no processo oxidativo e determinarão a aptidão física e cardiorrespiratória das crianças com e sem

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síndrome metabólica e que avaliarão a relação da obesidade e da resistência à insulina com a deficiência de vitamina A e seu ligante RBP-4; 3) ensaio clínico que avaliará os efeitos da suplementação de vitamina D e vitamina A e de outros nutrientes e não nutrientes da alimentação, além dos efeitos de protocolos de exercícios físicos, sobre os fatores antropométricos e bioquímicos de crianças com e sem síndrome metabólica ou com e sem excesso de peso corporal. Os critérios de inclusão no estudo serão: ter idade entre 4 e 11 anos, residir em Santo Antônio de Goiás, estar matriculado em escolas do ensino básico e fundamental do município e não ter doenças como alergias, deficiências cognitivas e físicas, além de doenças respiratórias crônicas e cardiológicas graves, que impeçam a coleta de dados e a participação nos estudos de intervenção.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar o efeito de programas de exercício físico e nutricional sobre as respostas metabólicas, oxidativas e inflamatórias em escolares de 4 a 11 anos de idade.

Objetivos Secundários:

- Caracterizar o nível sócio demográfico e nível de atividade física de crianças de Santo Antônio de Goiás;
- Estimar a composição corporal e aptidão cardiorrespiratória das crianças antes e após aplicação dos programas de intervenção;
- Diagnosticar crianças com e sem síndrome metabólica;
- Calcular a prevalência da síndrome metabólica entre as crianças;
- Medir níveis séricos de enzimas relacionadas ao processo oxidativo e inflamatório e analisar a sua relação com a aptidão cardiorrespiratória e os componentes da síndrome metabólica, antes e após aplicação dos programas de intervenção;
- Avaliar os aspectos relacionadas a qualidade de vida dos escolares, antes e após aplicação dos programas de intervenção;
- Medir níveis séricos de vitamina A e da proteína RBP-4 e associá-los com o consumo alimentar, em crianças obesas, não-obesas e com resistência à insulina;
- Medir níveis séricos de vitamina D em crianças e associá-lo com o consumo alimentar e com a síndrome metabólica e seus componentes;
- Investigar os efeitos da suplementação de vitamina D e de programas de educação nutricional e de

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exercícios físicos na síndrome metabólica e seus componentes.

Avaliação dos Riscos e Benefícios:

Riscos:

Esse trabalho poderá acarretar em desconforto (dor, ardência, edema, eritema, cansaço e fadiga) no momento da coleta de sangue e durante os testes de campo e de esteira. Contudo serão tomadas medidas para minimizar e tratar qualquer desconforto.

Benefícios:

Os participantes, juntamente com os pais ou responsáveis, terão acesso aos resultados da avaliação física, pressão arterial, consumo alimentar e exames bioquímicos, os quais servirão para diagnosticar problemas de saúde. Neste caso, os pais ou responsáveis receberão orientações para prevenção e tratamento das alterações diagnosticadas. Ainda, o estudo propõe a identificação de alterações metabólicas e moleculares, associadas à síndrome metabólica, que podem nortear políticas de prevenção, principalmente da obesidade, desde a idade escolar, incutindo nestes escolares hábitos de vida saudáveis.

Comentários e Considerações sobre a Pesquisa:

- Cronograma apresenta-se adequado, com indicação de recrutamento dos voluntários a partir de 08 de maio de 2017 e início de coleta de dados a partir de 05 de junho de 2017 (no documento Informações Básicas da Pesquisa). No arquivo do projeto, indicam-se início de recrutamento e coleta de dados a partir do mês de maio de 2017.
- Em parecer anterior foi recomendado: "Retirar o item CONSENTIMENTO DA PARTICIPAÇÃO DA PESSOA COMO VOLUNTÁRIO DA PESQUISA do questionário sociodemográfico. O consentimento é obtido por meio da assinatura do TCLE". Entretanto, essa recomendação NÃO foi atendida.
- Nesta nova submissão, dois subprojetos foram adicionados ao protocolo: 1) Efeitos de um programa de exercícios físicos em crianças de 4 a 11 anos de idade, com sobrepeso e obesidade, de Santo Antônio de Goiás-GO; e 2) Educação alimentar e nutricional e fatores de risco para a síndrome metabólica em crianças dos 4 aos 11 anos de idade. TCLEs e TALEs referentes a esses subprojetos foram também adicionados.
- As atividades de educação nutricional que serão realizadas foram descritas no TCLE referente ao subprojeto "Educação alimentar e nutricional e fatores de risco para a síndrome metabólica em crianças dos 4 aos 11 anos de idade", conforme solicitado no parecer anterior.
- Foram apresentados Termos de Compromisso assinados por todos os pesquisadores da equipe.

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- O pesquisador Felizardo Baltazar foi incluído na equipe de pesquisa.

Considerações sobre os Termos de apresentação obrigatória:

Nesta nova submissão, o protocolo foi instruído com os seguintes documentos: Informações Básicas da Pesquisa, Carta de Anuência da Secretaria Municipal de Educação de Santo Antônio de Goiás, Termos de Compromisso dos Pesquisadores, Questionários, Projeto de Pesquisa, Folha de Rosto da CONEP, Declaração da Pesquisadora comprometendo-se em entregar carta de anuência da escola em que será realizada a pesquisa, Carta Resposta às Pendências, TCLEs e TALEs referentes à cada subprojeto.

Conclusões ou Pendências e Lista de Inadequações:

As pendências indicadas no parecer anterior foram atendidas. Considera-se o projeto aprovado, smj deste Comitê.

Considerações Finais a critério do CEP:

Informamos que o Comitê de Ética em Pesquisa/CEP-UFG considera o presente protocolo APROVADO, o mesmo foi considerado em acordo com os princípios éticos vigentes. Reiteramos a importância deste Parecer Consubstanciado, e lembramos que o(a) pesquisador(a) responsável deverá encaminhar ao CEP-UFG o Relatório Final baseado na conclusão do estudo e na incidência de publicações decorrentes deste, de acordo com o disposto na Resolução CNS n. 466/12. O prazo para entrega do Relatório é de até 30 dias após o encerramento da pesquisa, prevista para dezembro de 2019.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_812089.pdf	16/03/2017 15:56:28		Aceito
Outros	atendimentopedencia.pdf	16/03/2017 15:55:19	Maria Sebastiana Silva	Aceito
Declaração de Pesquisadores	Termoscompromisso.pdf	16/03/2017 15:53:04	Maria Sebastiana Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLETALEAnaGabrielaa.pdf	16/03/2017 15:52:37	Maria Sebastiana Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de	TCLETALEAcaciaa.pdf	16/03/2017 15:52:23	Maria Sebastiana Silva	Aceito

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Ausência	TCLETALEAcaciaa.pdf	16/03/2017 15:52:23	Maria Sebastiana Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLETALEwendell.pdf	16/03/2017 15:52:09	Maria Sebastiana Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLETALEdiegoo.pdf	16/03/2017 15:51:50	Maria Sebastiana Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLETALEfelizardoo.pdf	16/03/2017 15:51:31	Maria Sebastiana Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLETALEneidianee.pdf	16/03/2017 15:51:14	Maria Sebastiana Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLETALEfagnerr.pdf	16/03/2017 15:50:54	Maria Sebastiana Silva	Aceito
Declaração de Instituição e Infraestrutura	Declaracaosecretariamunicipaleducacao.pdf	04/03/2017 09:19:47	Maria Sebastiana Silva	Aceito
Declaração de Pesquisadores	Termosdecompromisso.pdf	04/03/2017 09:07:27	Maria Sebastiana Silva	Aceito
Outros	cartadeatendimentodependencia.pdf	04/03/2017 09:06:31	Maria Sebastiana Silva	Aceito
Outros	Questionariosociodemografico.pdf	04/03/2017 08:51:40	Maria Sebastiana Silva	Aceito
Outros	Questionariodequalidadedevidaversaopais.pdf	04/03/2017 08:50:48	Maria Sebastiana Silva	Aceito
Outros	Questionariodequalidadedevidaversaocrianca.pdf	04/03/2017 08:49:49	Maria Sebastiana Silva	Aceito
Outros	Questionariodeatividadefisica7a11anos.pdf	04/03/2017 08:49:14	Maria Sebastiana Silva	Aceito
Outros	Questionariodeatividadefisica3a6anos.pdf	04/03/2017 08:48:41	Maria Sebastiana Silva	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoSantoAntonioCrian.pdf	04/03/2017 08:41:20	Maria Sebastiana Silva	Aceito
Declaração de Pesquisadores	Declaracaodopesquisadorresponsavel.pdf	04/03/2017 08:35:07	Maria Sebastiana Silva	Aceito
Folha de Rosto	folhaderosto.pdf	21/11/2016 16:36:01	Maria Sebastiana Silva	Aceito

Situação do Parecer:

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Aprovado

Necessita Apreciação da CONEP:
Não

GOIANIA, 18 de Março de 2017

Assinado por:
João Batista de Souza
(Coordenador)

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Anexo 2 – *Physical Activity Questionnaire for Older Child*ren (PAQ-C)

TEMPO DE PRÁTICA DE JOGOS E BRINCADEIRAS AO AR LIVRE

1. Num dia da semana (segunda a sexta-feira), quanto tempo seu filho(a) gasta brincando ou jogando ao ar livre, nos jardins, no quintal ou nas ruas ou no entorno da casa onde mora (ou da casa de vizinhos ou parentes)?

Da hora que acorda até o meio-dia	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■
Do meio-dia até as seis da tarde	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■
Das seis da tarde até a hora de dormir	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■

2. Num dia de final de semana (sábado e domingo), quanto tempo seu filho(a) gasta brincando ou jogando ao ar livre, nos jardins ou nas ruas ou no entorno da casa onde mora (ou da casa de vizinhos ou parentes)?

Da hora que acorda até o meio-dia	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■
Do meio-dia até as seis da tarde	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■
Das seis da tarde até a hora de dormir	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■

1. Num dia da semana (segunda a sexta-feira), quanto tempo seu filho(a) gasta assistindo televisão?

Da hora que acorda até o meio-dia	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■
Do meio-dia até as seis da tarde	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■
Das seis da tarde até a hora de dormir	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■

2. Num dia de final de semana (sábado e domingo), quanto tempo seu filho(a) gasta assistindo televisão?

Da hora que acorda até o meio-dia	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■
Do meio-dia até as seis da tarde	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■
Das seis da tarde até a hora de dormir	0 min ■	1-15 min ■	16-30 min ■	31-60 min ■	>60 min ■

Anexo 3 – Normas de publicação dos respectivos periódicos

Artigo 1 - Nutrition, Metabolism & Cardiovascular Diseases

Introduction

Cover letter, Article types

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Cover letters must state that all authors have seen and approved the study submitted.
Provide a statement that no part of the work submitted has been published or is under consideration for publication elsewhere (except in the form of abstract).
Provide a statement of financial or other relationships that might lead to a conflict of interest.
In the case of clinical trials, provide the registration number and date (see **Guidelines on Clinical Trials Registration** below).

TYPES OF MANUSCRIPT

Original Articles should report original clinical studies or research not previously published or being considered for publication elsewhere. The text should not exceed 4000 words, including list of authors and their affiliations, corresponding author, acknowledgements, key words and figure legends, with an abstract of maximum 250 words, a list of no more than 60 references, and maximum 6 figures/tables (see below for more details on the layout).

Systematic Reviews are exhaustive, critical assessments of evidence from different data sources in relation to a given subject in the areas of diagnosis, prevention and treatment of clinical disorders or public health issues relevant to the NMCD readership.
A systematic search of the relevant data sources should be carried out and the items collected should be carefully evaluated for inclusion based on a-priori defined inclusion/exclusion criteria. A description and an analytical graphic representation of the process should be provided. The specific features of the participants' or patients' populations of the studies included in the review should be described as well as the measures of exposure and outcome with the indication of the corresponding data sources. A structured abstract is required (like for Short reviews). The text must not exceed 6000 words including the acknowledgments, with no more than 8 tables and/or figures and maximum 120 references.

Meta-analyses should follow the same guidelines as for systematic reviews. They are expected to provide exhaustive information and statistical assessment of pooled estimates of pre-defined outcomes, study heterogeneity and quality, possible publication bias, meta-regression and subgroup analyses when appropriate. Depending on the type of study, Authors are invited to submit PRISMA flow

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Both systematic reviews and meta-analyses will be dealt with ordinarily as original articles as far as the editorial process is concerned.

Viewpoints and short review articles are generally upon invitation but authors interested in submitting a proposal are welcome to contact the editors. These articles also undergo peer review. Their length should not exceed 4000 words and should have an abstract of up to 250 words. A limit of 80 references is recommended.

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2. Registration must be done on a publicly available database, such as www.clinicaltrials.gov or any other registry meeting WHO and ICTRP criteria (please refer to http://www.who.int/ictrp/en/ or http://www.icmje.org/).

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

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One author has been designated as the corresponding author with contact details:
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AUTHOR INFORMATION PACK

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Data statement
To foster transparency, we encourage you to state the availability of your data in your submission. This may be a requirement of your funding body or institution. If your data is unavailable to access or unsuitable to post, you will have the opportunity to indicate why during the submission process, for example by stating that the research data is confidential. The statement will appear with your published article on ScienceDirect. For more information, visit the Data Statement page.

AFTER ACCEPTANCE

Online proof correction
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APÊNDICES

Apêndice 1 – TCLE e TALE

UNIVERSIDADE FEDERAL DE GOIÁS
FACULDADE DE EDUCAÇÃO FÍSICA E DANÇA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO – TCLE

O(A) seu(sua) filho(a) está sendo convidado(a) a participar como voluntário(a), de uma pesquisa chamada "Efeitos da suplementação de vitamina D sobre os fatores antropométricos e bioquímicos de crianças com e sem síndrome metabólica". Meu nome é Ana Gabriella Pereira Alves, sou a pesquisadora responsável e minha área de atuação é Nutrição. Após receber os esclarecimentos e as informações a seguir, se você aceitar que seu(sua) filho(a) faça parte do estudo, assine ao final deste documento, que está impresso em duas vias, sendo que uma delas é sua e a outra pertence à pesquisadora responsável. Esclareço que em caso de recusa na participação você não será penalizado(a) de forma alguma. Mas se aceitar participar, as dúvidas sobre a pesquisa poderão ser esclarecidas pelo pesquisador responsável, via e-mail (anagabriela_alves@hotmail.com) e, inclusive, sob forma de LIGAÇÃO A COBRAR, através do(s) seguinte(s) contato(s) telefônico(s): (62)3521-1256/(62)981742123. Ao persistirem as dúvidas sobre os direitos do seu (sua) filho (a) como participante desta pesquisa, você também poderá entrar em contato com o **Comitê de Ética em Pesquisa** da Universidade Federal de Goiás, pelo telefone (62)3521-1215.

INFORMAÇÕES IMPORTANTES SOBRE A PESQUISA

A Síndrome Metabólica (SM) representa uma situação clínica caracterizada por aumento da pressão arterial, da gordura e açúcar no sangue e obesidade, entre outros problemas, que são fatores de risco para as doenças do coração. Esta pesquisa é importante por causa da relação dessa doença com a quantidade de vitamina D no sangue.

Serão avaliadas crianças entre 4 a 11 anos que aceitarem participar da pesquisa. Todas as crianças receberão suplementação de vitamina D.

Os encontros da criança com os pesquisadores serão agendados conforme a disponibilidade da escola, da criança e dos pais ou responsáveis, na seguinte ordem:

1 – No primeiro dia agendado, a criança acompanhada de um responsável responderá perguntas sobre o consumo alimentar e exposição solar. Neste dia será entregue o primeiro suplemento de vitamina D, que durará 45 dias.

Depois deste encontro, o pesquisador ligará mais duas vezes para o pai ou responsável pela criança para saber como foi o dia alimentar do seu filho (a).

2 – Após a entrega do suplemento, será agendado um novo encontro 45 depois para a entrega de um novo frasco do suplemento de vitamina D e para aferição das medidas antropométricas (peso, altura, circunferência da cintura, pressão arterial e quantidade de gordura corporal). Neste dia também será realizado um recordatório alimentar.

3 – Após 45 dias da entrega do segundo frasco de suplemento, será realizada coleta de sangue do (a) seu (sua) filho (a), além da aferição das medidas antropométricas e avaliação do consumo alimentar.

4 – Após a coleta de sangue, haverá um intervalo de 3 meses e meio da pesquisa, onde após esse período haverá nova coleta de sangue e seu (sua) filho (a) voltará a receber novamente, por mais 3 meses, o suplemento de vitamina D, repetindo as avaliações descritas nos itens 1, 2 e 3.

5 – A participação de seu filho ou filha no estudo terá duração de nove meses e meio, sendo 6 meses de ingestão do suplemento de vitamina D.

Serão fotografadas imagens durante os encontros, havendo a necessidade de autorização de uso das fotos para divulgação em trabalhos e em congressos. Todas as avaliações serão feitas por profissionais capacitados para evitar qualquer incômodo como dor ou qualquer tipo de ferimento. Vale ressaltar que o incômodo que esta pesquisa acarretará será a coleta de sangue, porém este procedimento será realizado por profissional capacitado. Caso ocorra qualquer dano, a criança receberá tratamento adequado na Unidade Básica de Saúde.

Todas as informações obtidas serão mantidas em segredo. Este estudo trará informações importantes sobre a deficiência de vitamina D e sua relação com a síndrome metabólica, em crianças residentes em Santo Antônio de Goiás.

A participação na pesquisa é livre e não envolve nenhum custo, e não fornecerá nenhum tipo de pagamento ou gratificação financeira pela participação. A participação da criança **NÃO É OBRIGATÓRIA,** e o senhor(a) terá total liberdade

de, a qualquer momento, desistir da coleta de dados, sem que isto lhe traga, ou à criança, qualquer penalidade ou prejuízo.

Esta via fica com o pesquisador, não entregar para os pais:

CONSENTIMENTO DA PARTICIPAÇÃO DA PESSOA COMO VOLUNTÁRIO DA PESQUISA

Eu, ..., RG/CPF/n.º de prontuário/n.º de matrícula ....., abaixo assinado, autorizo a participação de meu (minha) filho (a) no estudo "Efeitos da suplementação de vitamina D sobre os fatores antropométricos e bioquímicos de crianças com e sem síndrome metabólica". Informo que sua participação nesta pesquisa é de caráter voluntário. Fui, ainda, devidamente informado(a) e esclarecido(a), pela pesquisadora responsável Ana Gabriella Pereira Alves, sobre a pesquisa, os procedimentos e métodos nela envolvidos, assim como os possíveis riscos e benefícios decorrentes de minha participação no estudo. Foi-me garantido que posso retirar meu consentimento a qualquer momento, sem que isto leve a qualquer penalidade. Declaro, portanto, que concordo com a participação do(a) meu(minha) filho(a) no projeto de pesquisa acima descrito.

( ) Permito a divulgação da imagem do meu (minha) filho (a) nos resultados que serão apresentados, por meio de palestras e recursos áudio visuais, aos responsáveis e demais moradores do município, bem como demais meios de comunicação, como forma de divulgação dos programas executados e seus resultados;
( ) Não permito a publicação da minha imagem do meu (minha) filho (a) nos resultados publicados da pesquisa.

Goiânia, ... de ..... de .....

Nome da criança: _____

_____

Assinatura por extenso do (a) pai (mãe) ou responsável

_____

Assinatura por extenso do(a) pesquisador(a) responsável

_____

Testemunhas em caso de uso da assinatura datiloscópica

UNIVERSIDADE FEDERAL DE GOIÁS
FACULDADE DE EDUCAÇÃO FÍSICA E DANÇA
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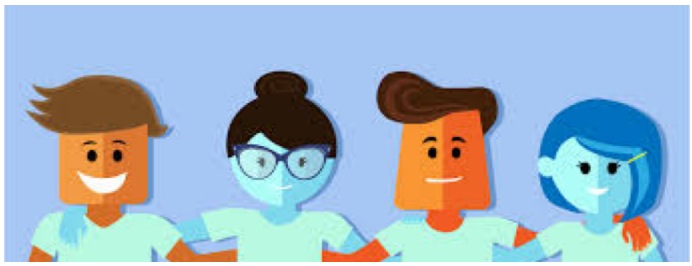
Termo de Assentimento Livre e Esclarecido - TALE

Olá criança, você é muito importante para nós e por isso estamos te convidando para fazer parte da nossa pesquisa chamada "Efeitos da suplementação de vitamina D sobre os fatores antropométricos e bioquímicos de crianças com e sem síndrome metabólica". A pesquisa será realizada pela equipe formada pela professora e estudantes da Universidade Federal de Goiás. A Ana Gabriella Alves é a responsável pela pesquisa.



Procedimentos: Está é uma pesquisa com objetivo de identificar uma doença chamada síndrome metabólica, causada pelo peso elevado. Além disso, vamos analisar o efeito da suplementação da vitamina D sobre essa doença. Para isso, precisaremos fazer algumas avaliações, como:

Medir o peso, altura, circunferência da cintura e quantidade de gordura:

Entrevista sobre como está a sua alimentação:

Coleta de sangue: **Medir a pressão do sangue:** **Tomar vitamina D:**

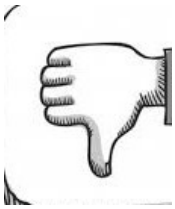
Esse trabalho não oferece risco à sua saúde, somente um pequeno desconforto no momento da coleta de sangue, que será realizada por profissionais capacitados.

Você não precisará gastar nenhum dinheiro para participar da pesquisa.

A pesquisa será importante para saber como está sua saúde e para prevenir a doença chamada síndrome metabólica, que tem relação com o peso elevado. A pesquisa não é obrigatória, você pode desistir da participação a qualquer momento sem ser prejudicado. Seus dados não serão divulgados para ninguém, sendo utilizados somente para fins dessa pesquisa e publicados, junto com imagens que serão fotografadas durante os encontros, em revistas, trabalhos e eventos.

Pintar o dedo que corresponde à sua resposta:

 Aceito participar da pesquisa

 Não aceito participar da pesquisa

Nome do(a) pai/mãe ou responsável: _____

Apêndice 2 – Ficha de acompanhamento de ingestão do suplemento de vitamina D

NOME DA CRIANÇA: _____

OBSERVAÇÃO: TOMAR TODOS OS DIAS, SEMPRE APÓS O ALMOCO! CASO SE ESQUEÇA DE DAR O SUPLEMENTO PRO SEU FILHO NESTE HORÁRIO, DAR ASSIM QUE SE LEMBRAR!

TOMAR 5 (CINCO) GOTAS AO DIA, DIRETO NA BOCA!

DATA								
TOMOU SUPLEMENTO (marcar X)								
HORÁRIO APÓS O ALMOÇO								

DATA								
TOMOU SUPLEMENTO (marcar X)								
HORÁRIO APÓS O ALMOÇO								

EM CASO DE DÚVIDA, ENTRAR EM CONTATO COM ANA GABRIELLA POR TELEFONE.

Apêndice 3 – Questionário sociodemográfico e econômico

Identificação

Data: _____

Nome da criança: _____

Data de nascimento: _____ Idade: _____

Sexo: ( ) F ( ) M

Raça: ( ) Branco ( ) Negro ( ) Pardo ( ) Amarelo

Número de pessoas, incluindo a criança, que moram na mesma casa: _____

Renda total da família que reside na mesma casa, incluindo salário, aposentadoria, pensões e outros rendimentos (como aluguéis, etc.):

( ) menor que 1 salário mínimo

( ) 1 a 2 salários mínimos

( ) 2 ou mais salários mínimos

Apêndice 4 – Questionário de exposição solar e uso de protetor solar

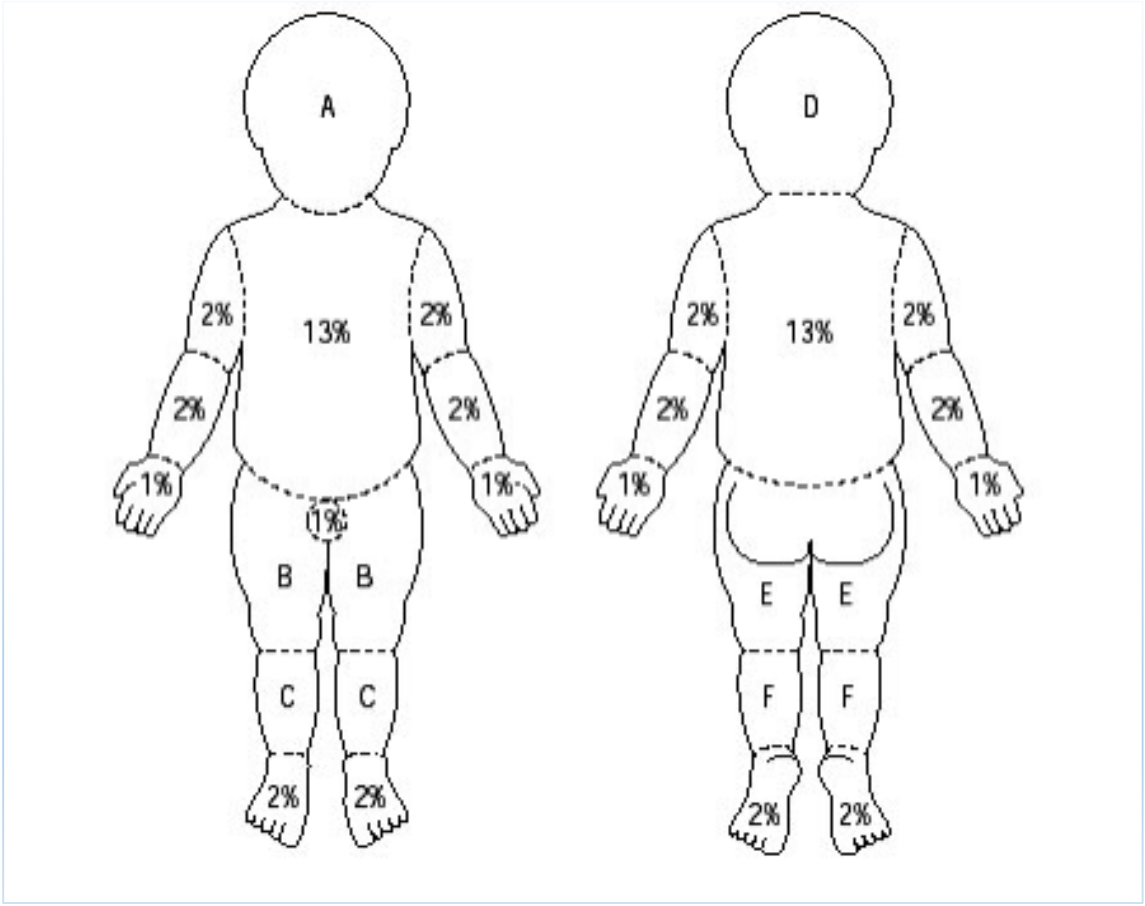
Data: _____

Nome completo da criança: _____

Nome do responsável: _____

Quais áreas do corpo do seu filho costumam ficar diariamente expostas ao sol?
Pintar cada parte do corpo na figura abaixo:

FRENTE COSTAS



1) Antes de se expor ao sol, você aplica protetor solar no seu filho:
   - ☐ Todos os dias
   - ☐ Apenas quando vai à praia/piscina/rio
   - ☐ Nunca
   - ☐ Outros:_____

Apêndice 5 – Recordatório alimentar

RECORDATÓRIO ALIMENTAR

Data: _____

Nome do pesquisador: _____
Nome da criança: _____

Recordatório de 24h (dia anterior)

Refeições	Alimentos/preparações	Medida Caseira
Café-da-manhã Horário: Local:		
Colação Horário: Local:		
Almoço Horário: Local:		
Lanche Horário: Local:		
Jantar Horário: Local:		
Ceia Horário: Local:		