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REBECCA PEIXOTO PAES SILVA

VITAMINAS LIPOSSOLÚVEIS, EXCESSO DE PESO E ESTADO INFLAMATÓRIO EM ADOLESCENTES

RECIFE-PE
2016

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Tese apresentada ao Programa de Pós-graduação em Nutrição do Centro de Ciências da Saúde da Universidade Federal de Pernambuco, para obtenção do título de Doutor em Nutrição.

Orientador: Dra. Célia Maria Machado Barbosa de Castro

Co-Orientador: Dra. lma Kruze Grande de Arruda

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Banca Examinadora:

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Dra. Ana Célia Oliveira dos Santos/ UPE

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Dra. Cristiane Pereira da Silva /UNIVERSO

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Dr. Marina de Moraes Vasconcelos Petribu/ UFPE

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Dra. Maria da Conceição Chaves de Lemos/ UFPE

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Dr. Pedro Israel Cabral de Lira /UFPE

Recife-PE

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À Deus,
que está sempre me ensinando
a manter a fé.

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"Tudo é considerado impossível até acontecer".

(Nelson Mandela)

RESUMO

A adolescência é um período nutricionalmente vulnerável, e dados atuais demonstram um aumento na prevalência de excesso de peso nesta faixa etária, associada a uma provável deficiência de micronutrientes, como as vitaminas lipossolúveis. A obesidade tem sido associada a um quadro inflamatório crônico de baixa intensidade, e evidências sugerem que na maior adiposidade e na presença de inflamação pode ocorrer diminuição da concentração das vitaminas lipossolúveis entre os adolescentes. Neste trabalho foi investigado a prevalência e os fatores associados à deficiência das vitaminas A, D, E e β-caroteno entre adolescentes escolares do nordeste do Brasil. Foi verificado também a associação entre estado inflamatório, adiposidade e as concentrações das vitaminas lipossolúveis nos adolescentes. Para tal, foi realizado um estudo transversal nas escolas públicas da cidade do Recife envolvendo adolescentes na faixa etária de 12 a 19 anos, de ambos os sexos, no período de março a abril de 2013. Foram excluídos os adolescentes que faziam uso farmacológico de vitamina A, D, E ou polivitamínicos, nos últimos 3 meses. A coleta dos dados foi realizada mediante aplicação de questionário abordando variáveis sócio-demográficas, estilo de vida e de consumo alimentar dos adolescentes. Em seguida, realizou-se a avalição antropométrica e coleta de sangue para análise das concentrações séricas de α-1-glicoproteína ácida (AGA), retinol, β-caroteno, α-tocoferol e 25-hidroxivitamina D (25(OH)D). Os resultados encontrados indicam que os adolescentes apresentam inadequação na ingestão da vitaminas A (50,3%), E (94,0%) e D (99,8%), assim como insuficiência/deficiências dos níveis séricos do α-tocoferol (88,1%), β-caroteno (74,1%), 25(OH)D (50,9%) e retinol (46,6%). Foi observado também maior risco de deficiência do α-tocoferol nas meninas (RP=1,11), e maior risco de insuficiência de 25(OH)D nos meninos (RP=1,41), bem como maior probabilidade de insuficiência do β-caroteno (RP=1,14) e da 25(OH)D (RP=1,38) no excesso de peso. Os níveis de AGA foram maiores na presença da obesidade abdominal nos adolescentes de ambos os sexos. Segundo avaliação pelo sexo, os meninos com níveis séricos de α-tocoferol insuficientes expressaram níveis reduzidos de AGA (p=0,03), e apresentaram um maior risco de deficiência de 25(OH)D e β-caroteno na adiposidade total e abdominal, enquanto as meninas mostraram maior risco de insuficiência de β-caroteno com a obesidade abdominal. Com isso, conclui-se que os adolescentes apresentam um risco potencial na inadequação das vitaminas lipossolúveis, e fatores como sexo e excesso de peso parecem interferir nas concentrações séricas destas vitaminas. Além disso, a adiposidade abdominal reflete um maior risco de inflamação, e causa alterações distintas nas concentrações das vitaminas lipossolúveis, de acordo com o sexo. No entanto, investigações futuras são necessárias para melhor compreensão do comportamento dessas vitaminas nos adolescentes frente a adiposidade e inflamação.

Palavras chave: Vitaminas lipossolúveis, Adolescentes, Inflamação, Excesso de peso

ABSTRACT

Adolescence is a nutritionally vulnerable period, and current data demonstrate an increase in the prevalence of overweight in this age group, associated with a possible deficiency of micronutrients, such as fat-soluble vitamins. Obesity has been associated with a chronic inflammatory condition of low intensity, and evidence suggests that in fat and higher in the presence of inflammation may occur decreasing the concentration of fat-soluble vitamins among teenagers. This work investigated the prevalence and factors associated with deficiency of vitamins A, D, E and β-carotene among school adolescents in northeastern Brazil. It was also verified the association between inflammatory state, adiposity and the concentrations of the fat-soluble vitamins in adolescents. To this end, we conducted a cross-sectional study in public schools in the city of Recife involving adolescents aged 12-19 years, of both sexes, from March to April 2013. teenagers who were pharmacological use of vitamin were excluded A, D, E or multivitamins, in the past 3 months. Data collection was conducted through a questionnaire covering socio-demographic, lifestyle and food consumption of adolescents. Then there was the anthropometric APPRAISAL and blood collection for analysis of serum acid α-1-glycoprotein (AGA), retinol, β-carotene, α-tocopherol and 25-hydroxyvitamin D (25 (OH) D) . The results indicate that adolescents have inadequate intake of vitamins A (50.3%), and (94.0%) and D (99.8%), and failure / shortcomings of serum α-tocopherol levels (88.1%), β-carotene (74.1%), 25 (OH) D (50.9%) and retinol (46.6%). It was also observed higher risk of deficiency of α-tocopherol in girls (PR = 1.11), and increased risk of insufficient 25 (OH) D in boys (PR = 1.41) and greater likelihood of β failure -carotene (OR = 1.14) and 25 (OH) D (OR = 1.38) in overweight. AGA levels were higher in the presence of abdominal obesity in adolescents of both sexes. According to evaluation by sex, boys with insufficient α-tocopherol serum levels expressed low levels of AGA (p = 0.03), and had a higher risk of deficiency of 25 (OH) D and β-carotene in the total and abdominal adiposity while girls showed a greater risk of failure of β-carotene with abdominal obesity. Thus, it is concluded that adolescents present a potential inadequacy of the fat-soluble vitamins, and factors such as sex and overweight seem to interfere in serum concentrations of these vitamins. Furthermore, abdominal adiposity reflects an increased risk of inflammation and causes different changes in the concentrations of fat-soluble vitamins, according to sex. However, future research is needed to better understand the behavior of these vitamins in adolescents in adiposity and

inflammation.

Keywords: Fat-soluble vitamins, Adolescents, Inflammation, Overweight

LISTA DE ABREVIATURAS E SIGLAS

25(OH)D – 25-Hidroxivitamina D

ABEP – Associação Brasileira de Empresas de Pesquisa

AGA – α-1-glicoproteína ácida

CC – Circunferência da Cintura

EROs – Espécies Reativas de Oxigênio

HPLC – Cromatografia Líquida de Alta Eficiência

IL – Inerleucina

IMC – Índice de Massa Corporal

MCP-1 – Proteína Quimiotática de Monócitos 1

OMS – Organização Mundial de Saúde

PCR – Proteína C reativa

PTH – Parathormônio

QFAA – Questionário de Frequência Alimentar para Adolescentes

RCA- Relação Cintura-Altura

RE – Retículo Endoplasmático

RFA – Resposta de Fase Aguda

TNF-α – Fator de Necrose Tumoral Alfa

SUMÁRIO

1. APRESENTAÇÃO

A adolescência é um período marcado por transformações físicas aceleradas, que são influenciadas por fatores hereditários, ambientais, nutricionais e psicológicos (LERNER, 1994). Todas essas transformações exercem efeito sobre o comportamento alimentar, influenciado por fatores internos (autoimagem, necessidades fisiológicas, preferências e desenvolvimento psicossocial) e por fatores externos (hábitos familiares, amigos, valores e regras sociais e culturais, mídia, modismos, experiências e conhecimentos do indivíduo) (FARTHING, 1991).

Os adolescentes, por apresentarem comportamento alimentar imediatista faz com que a sua atitude em relação à alimentação seja satisfatória no presente, não se interessando se a qualidade dos alimentos que consome possa vir a ser prejudicial na vida futura (MONTEIRO e JÚNIOR, 2007). Com isso, é bastante frequente o consumo de alimentos altamente palatáveis, ricos em açúcares e gorduras, e com teor reduzido em fibras e micronutrientes (IBGE, 2011; ARAÚJO et al, 2010).

Hábitos alimentares inadequados associado a modificação no estilo de vida tem contribuído para o aumento da frequência de obesidade em faixas etárias cada vez mais novas (PEREIRA e LOPES, 2012), favorecendo assim que o excesso de peso na infância esteja relacionado a um maior risco de morte prematura na vida adulta. Estudos relativamente recentes sugerem que a deficiência de micronutrientes podem contribuir para deposição de gordura e a inflamação crônica (GARCIA et al, 2013; ZAVALA et al, 2012), e um maior risco de baixas concentrações de vitaminas lipossolúveis tem sido observado em crianças e adolescentes obesos quando comparados às crianças e adolescentes com peso adequado (DE SOUZA et al, 2007; DECSI et al, 1997; MOLNAR et al, 2004).

Garcia e colaboradores (2013) ao investigar a associação entre concentrações de micronutrientes, obesidade, e inflamação crônica em crianças de 6 a 10,5 anos, de ambos os sexos, mostrou que indivíduos com baixas concentrações de vitamina A, C, E e zinco estavam associados à obesidade. Somado a isso, as crianças com sobrepeso ou obesidade e com baixas concentrações de vitamina A, C e E apresentaram concentrações elevadas de proteína C reativa (PCR), apresentando relação inversa entre eles. Os autores referiram que estes micronutrientes poderiam apresentar propriedades antiinflamatórias e exercer um papel importante na prevenção de doenças inflamatórias crônicas associadas à obesidade nos estágios iniciais da vida (GARCIA et al, 2013).

Evidências também sugerem que na obesidade pode ocorrer diminuição da concentração das vitaminas lipossolúveis no plasma devido a uma menor ingestão destes nutrientes e/ou maior deposição no tecido adiposo, que, por serem solúveis em gorduras, se depositam nos adipócitos, e assim, diminuem a biodisponibilidade em indivíduos com excesso de adiposidade (WORSTMAN et al, 2000). Além disso, as proteínas carreadoras das vitaminas se comportariam como proteínas negativas da fase aguda (ROSALES e ROSS, 1998), diminuindo assim sua disponibilidade no plasma durante processo inflamatório crônico existente na obesidade. Logo, a necessidade de um controle do estado inflamatório torna-se importante quando se deseja avaliar as concentrações séricas de vitaminas lipossolúveis.

Levando em consideração que as recomendações nutricionais atuais não levam em conta a biodisponibilidade das vitaminas lipossolúveis na presença da inflamação metabólica associada à obesidade, um estado crônico de inadequação destes micronutrientes podem colocar os adolescentes com excesso de peso num risco de desordem nutricional (ROOS, 2011; ROSS et al, 2011). Assim, torna-se necessário conhecer o comportamento das concentrações séricas das vitaminas no excesso de peso, visando remover a influência do estado inflamatório (THURNHAM et al, 2010; THURNHAM et al, 2003), o que justifica, mais uma vez, a relevância deste estudo.

Nesse sentido, a tese foi construída a partir da hipótese de que os adolescentes apresentarão, em sua maioria, consumo alimentar e concentrações séricas das vitaminas lipossolúveis inadequadas, e redução das concentrações plasmáticas de vitamina A, D, E e β-caroteno nos adolescentes com excesso de peso quando comparados aos adolescentes com peso adequado.

Logo, um dos objetivo do estudo foi estimar a prevalência e os fatores associados com a deficiência das vitaminas A, D e E entre adolescentes estudantes do nordeste do Brasil, sintetizado no artigo original "*Prevalence and associated factors to fat-soluble vitamins in adolescentes*", submetido à apreciação do corpo editorial para publicação no periódico *The American Journal of Clinical Nutrition*. Com o objetivo de investigar a associação entre adiposidade, inflamação e vitaminas lipossolúveis em adolescentes, foi elaborado o artigo original "*Adiposity, inflammation and fat-soluble vitamins in adolescents",* submetido à apreciação do corpo editorial para publicação no periódico *European Journal of Clinical Nutrition.*

A tese apresenta ainda, um ensaio bibliográfico, de base documental, a partir de artigos publicados em revistas científicas e sites governamentais, utilizando as bases de dados *SciElo, Lilacs e Medline,* no period de marco de 2012 a janeiro de 2016, bem como uma síntese conclusive dos resultados a partir da análise crítica do constructo teórico e dos achados da pesquisa empírica.

2. REVISÃO DA LITERATURA

2.1 Situação nutricional dos adolescentes brasileiros

A adolescência consiste no período de transição entre a infância e a idade adulta, caracterizada por um rápido e intenso crescimento físico, com profundas modificações orgânicas e comportamentais. Essas alterações são influenciadas por fatores hereditários, ambientais, nutricionais e psicológicos (KAZAPI et al, 2001). A Organização Mundial de Saúde (OMS) considera como adolescência a faixa etária compreendida entre 10 a 19 anos, sendo dividida em duas fases: fase inicial (10 a 14 anos) e fase final da adolescência (15 a 19 anos) (OMS, 1995). Na etapa inicial da adolescência começam as mudanças físicas, normalmente com uma aceleração repentina do crescimento, seguida pelo desenvolvimento dos órgãos sexuais e das características sexuais secundárias. Na fase final da adolescência, as principais mudanças físicas normalmente já ocorreram, embora o corpo ainda se encontre em desenvolvimento (UNICEF, 2011).

Neste interim, a nutrição tem papel fundamental, pois delimita condições favoráveis ao crescimento e desenvolvimento (SILVA et al, 2014), visto que nessa época da vida ganha-se 50% do peso peso final e 20 a 25% da estatura final (LOURENÇO e QUEIROZ, 2010). Como os hábitos dietéticos são estabelecidos na infância e adolescência e permanecem até a vida adulta (KELDER et al, 1994; LYTLE et al, 2000; LIEN et al, 2001), hábitos inadequados podem acarretar em consequencias a longo prazo, incluindo prejuizo na maturação sexual e baixa estatura na vida adulta (WHAL, 1999).

O padrão alimentar dos adolescentes, no entanto, apresenta-se em sua maioria inadequado, pois é comum entre esses indivíduos o consumo excessivo de *fast foods*, alimentos gordurosos, refrigerantes e açúcares, além da baixa ingestão de frutas, hortaliças e omissão de refeições, como o café-da-manhã (FISBERG, 2004; LEAL et al, 2010; ARAÚJO et al, 2010; IBGE, 2011). Tais características têm sido constantemente observadas tanto em estudos nacionais (VEREJA et al, 2013; PINHO et al, 2014; TAVARES et al, 2014) como em diversos países (TORNATIS et al, 2014; VORÁCOVÁ et al, 2015; WALTON et al, 2016).

É importante ressaltar que dietas inadequadas também estão envolvidas no surgimento de doenças crônicas não degenerativas no futuro, como obesidade, problemas cardiovasculares, hipertensão, diabetes e alguns tipos de câncer (WHO 2003). Neste sentido, Silva e colaboradores (2014) ao avaliarem o conhecimento dos adolescentes sobre alimentação e saúde, verificaram que tais indivíduos apresentavam bom entendimento sobre hábitos alimentares saudáveis e os problemas decorrentes dos maus hábitos. No entanto, os adolescentes entendem que estes problemas são desencadeados a longo prazo, e que, de modo geral, não acometem essa faixa etária. Esses dados demonstram que os adolescentes tem ciência de suas atitudes, no que diz respeito ao seu presente, porém não se preocupam com as consequências no seu futuro (SILVA et al, 2014), ou seja, os adolescentes comem por prazer, e não pelo que o alimento representa nutricionalmente (LEONARDO, 2009).

Emmett e Jones (2015), ao realizarem revisão de estudos longitudinais sobre alimentos e nutrientes ingeridos durante toda a infância e sua associação com o desenvolvimento da obesidade, observaram que as dietas mudaram drasticamente durante o período pré-escolar e manteve-se semelhante até a adolescência. A densidade energética da dieta mostrou uma forte associação com o aumento da gordura corporal entre as idades de 7 a 9 anos e entre as idades de 9 a 13 anos, e os fatores genéticos e dietéticos apresentaram associações independentes com o aumento da adiposidade.

No Brasil, assim como em diversas partes do mundo, com a transição nutricional, houve uma redução da prevalência dos déficits nutricionais e aumento do sobrepeso e obesidade, não só na população adulta, mas também em crianças e adolescentes (WANG et al, 2002). A obesidade está sendo considerada a mais importante desordem nutricional devido ao aumento de sua incidência. A prevalência da obesidade, a nível mundial, é tão elevada que a OMS considera esta doença como a epidemia global do século XXI (MONTEIRO, 2010).

A pesquisa Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico (Vigitel) de 2014 indica que o percentual de pessoas com excesso de peso supera mais da metade da população brasileira**,** referindo que 52,2% dos brasileiros estão acima do peso ideal e, destes, 16,8% são obesos (BRASIL, 2015). Somado a isso, o Estudo Internacional de Obesidade Infantil, desenvolvido em doze países, relata que cerca de 30% das crianças de dez anos têm obesidade ou sobrepeso. Os dados do Brasil, mostraram um índice de sobrepeso e obesidade de 39% entre as crianças avaliadas, representando um crescimento exponencial em comparação há 40 anos (KATZMARZYK et al, 2015). Estes dados demonstram que a obesidade atinge um número crescente de pessoas, e as atingem em idades cada vez mais novas (PEREIRA e CORREIA, 2012), favorecendo assim que excesso de peso na infância esteja relacionado a um maior risco de morte prematura na vida adulta.

Além disso, as deficiências de micronutrientes têm ganhado atenção dos pesquisadores pelo número crescente de evidências na literatura que comprovam seu impacto na morbimortalidade dos grupos de maior vulnerabilidade: as mulheres em idade fértil e as crianças (RAMALHO et al, 2008). Os adolescentes também são suscetíveis a deficiências nutricionais devido à demanda aumentada de nutrientes para atender ao intenso crescimento característico dessa fase, especialmente ferro, cálcio, zinco e vitaminas A, C, D, E e as do complexo B (SPEAR, 2002).

O estudo feito pela VIGITEL em 2014, revela que, dos mais de 40 mil brasileiros monitorados, apenas 24,1% consomem a quantidade recomendada de frutas e hortaliças o que, na prática, pode se refletir em deficiências nutricionais (BRASIL, 2015). No Brasil, existe uma grande limitação sobre dados acerca do status dos micronutrientes nas diversas faixas etárias, porém os achados do estudo de Veiga e colaboladores (2013) ao avaliarem o consumo de micronutrientes através do Inquérito Nacional de Alimentação, 2008-2009 em 6.797 adolescentes entre 10 e 18 anos, observaram uma grande inadequacão na ingestão de vitaminas e minerais, tanto no sexo feminino como masculino, com destaque de inadequação para o cálcio (>95%), fósforo (entre 54% e 69%), vitamina A (entre 66% e 85%), vitamina E (100%) e vitamina C (entre 27% e 49%).

Essa deficiência de micronutrientes, assim como o sobrepeso e a obesidade, são motivos de grande preocupação nos atuais cenários brasileiro e mundial, visto que tais desordens nutricionais cursam com impacto negativo sobre a saúde e pode influir sobre riscos de morbidade em curto prazo, com impacto significativo sobre a qualidade de vida em longo prazo (LAMOUNIER, 2009). Assim, os adolescentes são considerados vulneráveis em termos nutricionais, pois a demanda de nutrientes é maior devido ao aumento no crescimento e desenvolvimento físico. No entanto, em virtude das frequentes mudanças ocorridas no estilo de vida, a ingestão e a necessidade de nutrientes na adolescência nem sempre é alcançada (MAHAN et al, 2012).

2.2 Obesidade e inflamação

A obesidade é definida como acúmulo excessivo de gordura no organismo, sendo esta capacidade de armazenamento energética virtualmente ilimitada. A ausência de limite representa vantagem adaptativa a curto prazo, e desvantagem a longo prazo, traduzida em disfunção endócrina/metabólica (GREGOIRE, 2001; PRINS, 2002). Segundo a

Organização Mundial de Saúde (OMS), a obesidade pode ser compreendida como um agravo de caráter multifatorial decorrente de balanço energético positivo, associado a riscos para a saúde devido à sua relação com complicações metabólicas, como aumento da pressão arterial, dos níveis de colesterol e triglicerídeos sanguíneos e resistência à insulina (OMS, 2000).

Até relativamente pouco tempo, o papel da gordura em si no desenvolvimento da obesidade e suas consequências foi considerado passivo. O tecido adiposo, por muitos anos, foi visto somente como local de reserva energética, protetor contra choques e isolante térmico (TRAYHURN e WOOD, 2004; GREENBERG e MARTIN, 2006; GOOSSENS, 2008). Entretanto, após a descoberta de inúmeras substâncias secretadas pelos adipócitos, dentre elas hormônios e citocinas, esse tecido passou a ser visto como órgão dinâmico e suas funções inflamatória e endócrina foram evidenciadas (BERG, 2005; TRAYHURN et al, 2006; HAJER et al, 2008), e os estudos têm apontado a reação inflamatória como fator comum entre as doenças metabólicas, formando um elo entre adiposidade, síndrome metabólica e doenças cardiovasculares (FESTA et al, 2000; DANDONA et al, 2007).

O gatilho inflamatório na obesidade é metabólico e causado pelo consumo excessivo de nutrientes. Este estado metabólico inflamatório possui características únicas em comparação à inflamação clássica, e é definida por baixo grau de inflamação crônica, orquestrada pelas células metabólicas (tecido adiposo, fígado, músculo, pancreas e cérebro) em resposta ao excesso de nutrientes e energia (CAI, 2009; GREGOR e HOTAMISLIGIL, 2011).

A hipernutrição, com altos níveis circulantes de glicose, ácidos graxos livres, e aminoácidos, é o indutor patogênico predominante de inflamação metabólica central, visto que os nutrientes em excesso, quando transportados para as células, aumentam diretamente a carga de trabalho oxidativo mitocondrial, causando o aumento da produção mitocondrial de espécies reativas de oxigênio (EROs) pela cadeia transportadora de elétrons, conduzindo estresse oxidativo intracelular. Em paralelo, os altos níveis de atividades metabólicas celulares exigem aumento de síntese e enovelamento proteico pelo retículo endoplasmático (RE), levando ao estresse do RE. Além disso, altos níveis intracelulares de EROs provenientes do estresse oxidativo podem intensificar o estresse do RE, causando acúmulo intracelular de mitocôndrias, RE e proteínas citosólicas disfuncionais, levando ao aumento de estresse da autofagia e defeito autofágico (FRÓES, 2012).

Somado a isso, o processo de hipertrofia e hiperplasia dos adipócitos, decorrente do aumento do armazenamento de energia, condiciona situações de hipóxia dos adipócitos com consequente produção de EROs (MOURA e MONTEIRO, 2010). Os adipócitos hipertrofiados comprimiriam a vasculatura do tecido reduzindo a chegada de oxigênio. Em consequência à hipóxia, haveria um estímulo à produção de citocinas pró-inflamatórias a fim de aumentar a angiogênese e o fluxo sanguíneo (TRAYHURN e WOOD, 2004)

Assim, em resposta ao estresse oxidativo, decorrente da produção excessiva de EROs, os adipócitos aumentam a produção de citocinas pró-inflamatórias, e recrutamento de macrófagos para o tecido adiposo, que serão os responsáveis pela remoção dos produtos resultantes da lise dos adipócitos (CINTI et al, 2005; HOTAMISLIGIL, 2006; PASARICA et al, 2009).

O tecido adiposo secreta substâncias, tais como fator de necrose tumoral-α (TNF-α), interleucina-6 (IL-6), interleucina-8 (IL-8), proteína quimiotática de monócitos-1 (MCP-1), adiponectina, resistina e leptina, responsáveis por mediar a inflamação (BRUUNSGAARD et al, 2000; PICKUP, 2004; FONTANA et al, 2007) e alterar a sensibilidade à insulina, aumentar a liberação de moléculas de adesão pelo endotélio, aumentar a liberação hepática de fibrinogênio e efeito pró-coagulante nas plaquetas. Estes fatores poderiam assim justificar a associação da obesidade a um maior risco de desenvolvimento de doenças cardiovasculares e diabetes (HRICH et al, 1990; BANKS et al, 1995; PAPANICOLAU et al, 1998; YUDKIN et al, 2000).

As citocinas pró-inflamatórias são consideradas marcadores de atividade do processo inflamatório, e também indutoras da resposta de fase aguda (RFA), correspondente ao processo sistêmico da inflamação, verificando-se aumento da síntese hepática e dos níveis séricos das proteínas de fase aguda (MAEDA et al, 1995), principalmente a proteína C reativa (PCR), considerada o marcador mais sensível e específico da RFA, já que sua concentração no plasma reflete diretamente a intensidade do processo patológico. A indução da RFA é um reflexo da ação das citocinas inflamatórias e a alteração dos níveis dos seus marcadores no sangue periférico (SANTOS et al, 2000; PEPYS e HIRSCHFIELD, 2003).

Nesse sentido, o uso de biomarcadores preditivos do estado inflamatório tem sido testado e devidamente avaliado, principalmente a PCR, que tem comportamento semelhante à alfa-1-antiquimiotripsina, e a alfa-1-glicoproteína ácida (AGA), que é uma nova nomenclatura para o orosoromucóide. A PCR e a AGA parecem seguir padrões diferentes por ocasião da instalação de um quadro inflamatório. No início da inflamação a PCR aumenta rapidamente (≥ 5 mg/L) e atinge o seu pico entre 24 e 48 horas, enquanto que a AGA pode demorar até 4 a 5 dias para atingir o seu "plateau" (FLECK e MYERS, 1985). Quando a intensidade da inflamação diminui, a PCR cai rapidamente, enquanto que a AGA permanece elevada (> 1,0 g/L). Esse comportamento peculiar da AGA configura ao marcador uma maior validade para o diagnóstico do estado inflamatório.

2.3 Obesidade, inflamação e vitaminas lipossolúveis

Estudos recentes sugerem que a deficiência de micronutrientes podem contribuir para deposição de gordura e a inflamação crônica (ZAVALA et al, 2012; GARCIA et al, 2013). Um maior risco de baixas concentrações de vitaminas A, E e D tem sido observado em crianças e adolescentes obesos quando comparados às crianças e adolescentes com peso adequado (DECSI et al, 1997; MOLNAR et al, 2004; DE SOUZA et al, 2007).

Ao tentar investigar a associação entre concentrações de micronutrientes, obesidade e inflamação crônica em crianças de ambos os sexos, Garcia e colaboradores (2013) demostraram que indivíduos com baixas concentrações de vitamina A, C, E e zinco estavam associados à obesidade. Somado a isso, as crianças com sobrepeso ou obesidade e com baixas concentrações de vitamina A, C e E apresentaram concentrações elevadas de PCR, apresentando relação inversa entre eles. Os autores referiram que estes micronutrientes poderiam apresentar propriedades antiinflamatórias e exercer um papel importante na prevenção de doenças inflamatórias crônicas associadas à obesidade nos estágios iniciais da vida.

Tendo conhecimento que o tecido adiposo medeia a produção de citocinas e produtos oxidativos, Markovits e colaboradores (2009), ao investigar o efeito do licopeno, nos antioxidantes plasmáticos, marcadores inflamatórios e produtos oxidantes em obesos, verificaram uma correlação inversa entre carotenoides plasmáticos e IL-6 e PCR, confirmando que os carotenoides apresentam relação inversa com marcadores inflamatórios.

Estudos também referem que a vitamina D, de certa forma, influencia na patogênese da obesidade, uma vez que reduz a ação dos macrófagos na resposta inflamatória nos adipócitos humanos (DING et al, 2013), além de diminuir a liberação de MCP-1, IL-8 e IL-6 nos pré-adipócitos, interrompendo assim o ciclo vicioso do recrutamento dos macrófagos (GAO et al, 2013).

Nesse sentido, estudo desenvolvido por Smotkin-Tangorra e colaboradores (2007), envolvendo indivíduos obesos na faixa etária de 7 a 18 anos, de ambos os sexos, procedentes de uma Clínica de Endocrinologia Pediátrica, mostrou que 55,2% dos 217 pacientes tinham concentrações de vitamina D insuficientes (< 20 ng/mL) e que 21,6% tinham deficiência (≤10 ng/mL), e aqueles com menor concentração de vitamina D apresentavam IMC significativamente mais elevados.

Considera-se que o nível ótimo de vitamina D seria aquele necessário para manter o parathormônio (PTH) em níveis adequados, visto que a deficiência de vitamina D leva à diminuição do cálcio sérico, o qual, em consequência, estimula as glândulas paratireoides a liberar o PTH, a fim de elevar a reabsorção renal e óssea do cálcio (HOLLIS, 2005; CUNHA et al, 2014). Estudo retrospectivo desenvolvido em uma clínica para controle do peso corporal na Espanha observou que a prevalência de insuficiência ou deficiência de vitamina D aumentou a medida que se elevou o IMC, e a prevalência de hiperparatiroidismo aumentou de 12 %, entre os não obesos, para 47,5 % entre aqueles indivíduos com IMC maior que 50 kg/m^2. Baixas concentrações de vitamina D e altas concentrações do PTH mostraram-se associadas com o aumento do risco de síndrome metabólica e dislipidemia aterogênica. A análise de regressão mostrou que o IMC, a sazonalidade e a idade foram identificados como preditores independentes das concentrações de PTH e vitamina D (GUASCH et al, 2012).

Evidências sugerem que na obesidade pode ocorrer diminuição da concentração das vitaminas lipossolúveis no plasma devido a uma menor ingestão destes nutrientes e/ou maior deposição no tecido adiposo, que, por serem solúveis em gorduras, se depositam nos adipócitos, e assim, diminuem a biodisponibilidade em indivíduos com excesso de adiposidade (WORSTMAN et al, 2000). Entretanto, essa teoria de sequestro pelo tecido adiposo tem sido questionada, e Drincic e colaboradores (2012) relatam que a diluição da vitamina D na grande massa gorda de indivíduos obesos poderia plenamente justificar estas baixas concentrações.

Somado a isso, as proteínas carreadoras das vitaminas se comportariam como proteínas negativas da fase aguda (ROSALES e ROSS, 1998), diminuindo assim sua disponibilidade no plasma durante processo inflamatório crônico existente na obesidade. Logo, a necessidade de um controle do estado inflamatório é salutar quando se deseja avaliar as concentrações séricas de vitaminas lipossolúveis.

Levando em consideração que as recomendações nutricionais atuais não levam em conta a biodisponibilidade das vitaminas lipossolúveis na presença da inflamação metabólica associada à obesidade, um estado crônico de inadequação destes micronutrientes podem colocar os adolescentes com excesso de peso num risco de desordem nutricional (ROOS, 2011; ROSS et al, 2011). Assim, torna-se necessário estabelecer fatores de correção para as concentrações séricas, visando remover a influência do estado inflamatório (THURNHAM et al, 2003; THURNHAM et al, 2010).

3. JUSTIFICATIVA

A prevalência de sobrepeso e obesidade vem aumentando consideravelmente ao longo dos anos, inclusive nos indivíduos de faixas etárias mais jovens, cursando assim com o aumento de desordens nutricionais. Os adolescentes com excesso de peso constituem um grupo de alto risco para a deficiência de vitaminas lipossolúveis, em virtude de uma menor ingestão dos alimentos fontes destes nutrientes, bem como redução dos níveis plasmáticos decorrentes da maior deposição nos adipócitos. Sabendo também que os adolescentes com sobrepeso e obesidade apresentam inflamação crônica de baixa intensidade, a redução de nutrientes com ação anti-inflamatória ou imunomoduladora induziria maior liberação de citocinas inflamatórias e aumento do estresse oxidativo, contribuindo para um maior risco de desenvolvimento precoce de resistência à insulina e doenças cardiovasculares.

Tendo em vista que são escassos os dados sobre o status das vitaminas lipossolúveis em adolescentes com excesso de peso na região nordeste, assim como há um número reduzido de publicações acerca do comportamento destes nutrientes na inflamação, torna-se importante a compreensão a atuação dessas vitaminas na presença de inflamação e/ou excesso de peso entre os adolescentes. Diante disso, este estudo possibilitará a identificação do comportamento das concentrações de vitaminas lipossolúveis nos adolescentes, permitindo uma análise da adiposidade e/ou fator inflamatório quando avaliado as concentrações destas vitaminas.

4. HIPÓTESES

- Os adolescentes apresentam, em sua maioria, consumo alimentar e concentrações séricas das vitaminas lipossolúveis inadequadas.
- Os adolescentes com excesso de peso apresentam elevação da alfa-1-glicoproteína ácida e redução das concentrações plasmáticas de vitamina A, D, E e β-caroteno quando comparados aos adolescentes com peso adequado.

5. OBJETIVOS

5.1. Objetivo geral

Avaliar a influência do processo inflamatório crônico de baixa intensidade e do excesso de peso nos níveis séricos de vitaminas A, D, E e β-caroteno em adolescentes.

5.2. Objetivos específicos

- Avaliar o estado nutricional, consumo alimentar e o estilo de vida dos adolescentes;
- Estimar a prevalência de deficiência de vitamina A, D, E e β-caroteno em adolescentes;
- Avaliar os fatores de risco para deficiência das vitaminas A, D, E e β-caroteno
- Verificar o estado inflamatório dos adolescentes;
- Associar as concentrações das vitaminas A, D, E e β-caroteno no plasma com a alfa-1-glicoproteina ácida em adolescentes com excesso de peso.

6. METODOLOGIA

6.1 Desenho do estudo e casuística

Foi realizado um estudo transversal envolvendo adolescentes de 12 a 19 anos, de ambos os sexos, no período de março a abril de 2013. Este estudo foi aninhado em uma coorte prospectiva, com adolescentes recrutados de forma aleatória, por um processo de amostragem em poli etapas, nas escolas públicas da cidade do Recife, nordeste do Brasil. Foram excluídos os adolescentes que faziam uso farmacológico de vitamina A, D, E ou polivitamínicos, nos últimos 3 meses.

O tamanho da amostra baseou-se em uma prevalência estimada (p) de deficiência de a-tocoferol de 25%, um erro amostral (d) de 5,5%, um nível de 95% de confiança (z) e um efeito do desenho (c) de 2,1, considerando que a seleção da amostra foi por conglomerado. Utilizando-se a fórmula $n = (z^2 \times p \times q \times c) / d^2$, corrigida para população finita, resultou em um número de unidade amostral mínima de 370 indivíduos. Para corrigir eventuais perdas foi acrescido um percentual de 11% [100/(100-11)], resultando numa amostra de 416 adolescentes. A amostra final trabalhada foi de 411 adolescentes escolares.

6.2 Métodos e técnicas de avaliação

A coleta dos dados foi realizada mediante aplicação de questionário abordando variáveis sócio-econômicas, estilo de vida e de consumo alimentar dos adolescentes. As entrevistas para a obtenção dos dados dietéticos foram realizadas por uma equipe composta por duas técnicas e uma aluna da pós-graduação em nutrição da Universidade Federal de Pernambuco. Para assegurar a acurácia e fidedignidade dos dados, todos da equipe de pesquisa receberam treinamento e orientação sobre os procedimentos e a rotina de desenvolvimento do estudo. Em seguida, realizou-se a avalição antropométrica e coleta de sangue para análise das concentrações séricas de α-1-glicoproteína ácida, retinol, β-caroteno, α-tocoferol e 25-hidroxivitamina D.

6.3 Variáveis sóciodemográficas

Foram obtidas por meio de entrevista realizada na escola e/ou domicilio, abrangendo questões sobre sexo, idade e classificação socioeconômica. Na determinação do nível socioeconômico foram empregados os Critérios de Classificação Econômica do Brasil, classificada de acordo com os critérios da Associação Brasileira de Empresas de Pesquisa (ABEP, 2010). Esse instrumento utiliza uma escala de pontos, obtidos pela soma dos pontos da posse de itens domésticos e pelo grau de instrução do chefe da família, que classifica a população nas classes econômicas A1, A2, B1, B2, C1, C2, D e E, de ordem decrescente, respectivamente iniciada pelo de maior poder aquisitivo.

6.4 Variáveis relacionadas ao estilo de vida

Os adolescentes foram classificados, segundo os níveis de atividade física, em pouco ativos/sedentários ou em suficientemente ativos, de acordo com os critérios de Pate e colaboradores (2002). Na classificação dessa variável foi utilizado o ponto de corte recomendado por Suñé e colaboradores (2007), ou seja, 4 horas e 30 minutos/dia para o somatório de tempo despendido em atividades consideradas sedentárias. Foi classificado como tabagista o adolescente que referiu fumar uma quantidade maior ou igual a 5 cigarros/dia (PIEGAS et al, 2003). O adolescente que referiu ingerir quantidade de bebida alcoólica > 30 g/dia, no sexo masculino, e > 15 g/dia, no sexo feminino, foi considerado com hábito positivo de ingestão alcoólica (SBC, 2005).

6.5 Variáveis dietéticas

A verificação do consumo alimentar foi realizada pela aplicação de um questionário de frequência alimentar para adolescentes (QFAA) semiquantitativo, desenvolvido e validado por Slater et al. (2003), com adaptações para alimentos de uso comum na região. O QFAA apresenta perguntas relativas a frequência de consumo de 91 itens alimentares, contando com onze opções de frequência de consumo: nunca, uma a dez vezes por dia, semana ou mês.

O consumo dietético foi analisado pelo programa DietSys software versão 4.01 (National Cancer Institute, Bethesda, MD, USA), que utiliza como base de dados a Tabela de Composição Química dos Alimentos do Departamento de Agricultura dos Estados Unidos (USDA, 2001). Os resultados do consumo de vitamina A, D e E foram comparados com os valores da *Dietary Reference Intakes* (DRI's) propostos pelo Institute of Medicine (IOM, 2002).

6.6 Variáveis antropométricas

A avaliação antropométrica constou de dupla tomada do peso, altura e circunferência da cintura, sendo utilizada a média das duas aferições como resultado final. Para consistência dos dados, foram desprezadas as medidas que apresentaram diferenças superiores a 100g para o peso e 0,5 cm para a altura. As medidas de peso e altura foram realizadas segundo técnica original recomendada por Lohman e colaboradores (1988). A massa corporal foi obtida em balança eletrônica digital, da marca Plenna-MEA-03140®, com capacidade máxima de 150 Kg e precisão de 100g. A altura foi aferida com o uso de fita métrica Stanley® milimetrada, com precisão de 1 mm e exatidão de 0,5 cm. A CC foi obtida no ponto médio entre o último arco costal e a crista ilíaca, com fita métrica flexível e inelástica, sem comprimir os tecidos (TAYLOR et al, 2000). O diagnóstico nutricional dos adolescentes foi definido de acordo com curvas de IMC da OMS (DE ONIS, 2007). Para o diagnóstico da obesidade abdominal o ponto de corte utilizado para classificação da CC foi de Taylor e colaboradores (2000), e para Relação Cintura/Altura (RCA), foi utilizado o ponto de corte preconizado por Li e colaboradores (2006).

6.7 Variáveis bioquímicas

As análises bioquímicas foram realizadas após coleta de aproximadamente 10 mL de sangue por punção venosa, realizada na própria escola ou em domicilio, após jejum de 10 a 12 horas. Os frascos foram acondicionados em caixas de isopor contendo gelo reciclável, vedadas e transportadas para o processamento das amostras no laboratório de análises clínicas LAPAC, num prazo máximo de 2 horas. O soro foi separado das hemácias por centrifugação e acondicionado em dois tubos com 2mL. Imediatamente, uma das alíquotas do soro foi utilizado para analisar as concentrações de α-1-glicoproteína ácida e 25-hidroxivitamina D (25(OH)D). A outra alíquota foi congelada e posteriormente enviada ao Centro de Investigação em Micronutrientes (CIMICRON), da Universidade Federal da Paraíba (UFPB), para determinação das concentrações séricas de retinol, β-caroteno e α-tocoferol.

α-1-glicoproteina ácida

A α-1-glicoproteína ácida (AGA) foi quantificada por imunoturbidimetria utilizando reagentes, calibradores e controles Roche, em sistema automatizado Cobas mira (Roche). A presença de inflamação foi definida como valor acima de 0,9 g/L.

Retinol, β-caroteno e α-tocoferol

A quantificação dos níveis de retinol, β-caroteno e α-tocoferol sérico, seguiu o procedimento técnico descrito por Erhardt e colaboradores (2002), sendo utilizado o cromatrógrafo líquido (LC-10Avp, Shimadzu Corporation, Analytical Instruments Division, Kyoto, Japão), constituído de bomba (SCL-10Avp), detector UV-VIS munido de lâmpada de deutério (SPD-10Avp) e injetor manual; e controlado pelo programa de “software” Class-vp 6.12 SP5. A separação cromatográfica foi feita em coluna de fase reversa C18 (Shimadzu LC Columm – CLC-ODS “M” 25 cm; 4,6 mm ID X 25 cM – 5 μm).

A preparação das amostras para a injeção de 50μL no pela cromatografia liquida de alta resolução (HPLC, modelo 305, Gilson, França), consistiu em descongelamento do soro em temperatura ambiente, sendo este procedimento realizado na penumbra. Foram pipetados 100 μL de solução de extração (etanol) e 50 μL de soro em microtubo âmbar, homogeneizado, centrifugado e separados aproximadamente, 90 μL de sobrenadante, com posterior refrigeração até o momento de injetar no HPLC. Os comprimentos de onda estabelecidos pelo método para o α-tocoferol, retinol e β-caroteno foram, respectivamente, de 292 nm, 325 nm e 452 nm. O tempo de corrida ficou estabelecido em 4 minutos para o retinol e 22 minutos para o β-caroteno.

Utilizou-se os pontos de corte recomendados pela OMS para os níveis de retinol, considerando-se: deficiente: < 0,35 μmol/L; baixo: 0,35 a 0,69 μmol/L; aceitável: 0,70 a 1,04 μmol/L e normal: ≥ 1,05 μmol/L. A deficiência de vitamina A foi caracterizada quando os valores de retinol estiveram abaixo de 0,70 μmol/L. Para o α-tocoferol, utilizou-se como referencia valores ≥ 12 μmol/L (EFSA, 2015), enquanto os valores de β-caroteno foram considerados adequados nas concentrações > 0,9 μmol/L (PEREIRA et al, 2008).

25-hidroxivitamina D

A 25(OH)D foi dosada pelo método de Cromatografia líquida de alta eficiência (HPLC). A deficiência de vitamin D foi definida como um valor de 25(OH)D abaixo de 52,5 nmol/L e insuficiência os valores de 52,5 a 72,5 nmol/L (HOLICK et al, 2011).

6.8 Análise dos dados

Os dados foram digitados com dupla entrada e verificados com o VALIDATE, módulo do Programa Epi-Info, versão 6.0 [WHO/CDC, Atlanta, GE] para checar a consistência no processo de digitação. A análise estatística dos dados foi realizada com o auxílio do programa *Statistical Package for Social Sciences - SPSS* versão 13.0 (SPSS Inc., Chicago, IL).

Foi realizada análise exploratória dos dados (exclusão dos *outliers*); As variáveis contínuas foram testadas quanto à normalidade da distribuição, pelo teste de Kolmogorov

Smirnov (para avaliar a simetria da curva da distribuição das variáveis). Os dados das variáveis de distribuição normal foram expressos na forma de média e desvio padrão. As variáveis com distribuição não gaussiana foram apresentadas sob a forma de medianas e dos respectivos intervalos interquartílicos. Na descrição das proporções, a distribuição binomial foi aproximada à distribuição normal pelo intervalo de confiança de 95%.

Na análise univariada a força da associação entre a variável dependente, quando categorizada, com as variáveis independentes, foi avaliada pelas razões de prevalência e respectivos intervalo de confiança, além do teste do Qui quadrado de Pearson. Quando a variável dependente foi tratada como variável contínua, a sua associação foi testada pelo métodos paramétrico (Teste "*t*" de *Student* para dados não pareados ou ANOVA uma via), ou o seu equivalente não paramétrico (Teste U de Mann Whitney ou Teste de Kruskal Wallis), quando aplicável. Em todos os testes estatísticos foi utilizado o nível de significância de 5% para rejeição da hipótese de nulidade.

6.9 Aspectos éticos

O estudo foi submetido e aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos do Hospital Universitário Lauro Wanderley da Universidade Federal da Paraíba, Brasil (Registro CEP/HULW nº 723/10) (ANEXO 1), pautado pelas normas éticas para pesquisa envolvendo seres humanos, constantes na resolução vigente à época, 196/96 do Conselho Nacional de Saúde.

Os adolescentes e seus responsáveis foram previamente informados dos objetivos da pesquisa, bem como dos métodos a serem adotados. Mediante o seu consentimento, o responsável assinou um termo de consentimento livre e esclarecido. Foi garantido aos adolescentes e seus responsáveis, além do sigilo dos dados, o retorno dos resultados das avaliações realizadas. Os pesquisadores estiveram à disposição para esclarecimentos a qualquer dúvida acerca dos procedimentos, riscos, benefícios e demais dúvidas relacionadas com a pesquisa.

6.10 Fontes de Financiamento

Conselho Nacional de Pesquisa (CNPq) (processo n.473387/2010-2) e Ministério de Ciência e Tecnologia (convênio IMIP/MCT processo 01.0265.00/2005).

7. RESULTADOS – Artigos Originais

7.1 Artigo 1

<u>Tittle</u> **Prevalence and factors associated with fat-soluble vitamin deficiency in adolescents**

<u>Authors:</u> Rebecca Peixoto Paes-Silva[1], Marilia Tokiko Oliveira Tomiya[2], Maria da Conceição Chaves de Lemos[3], Célia Maria Machado Barbosa de Castro[4], Ilma Kruze Grande de Arruda[5], Alcides da Silva Diniz[5]

<u>Affiliation:</u> [1]Doctorate Student in Nutrition at the Universidade Federal de Pernambuco, Brazil; [2]Doctorate Student in Children and Adolescent Health at the Universidade Federal de Pernambuco, Brazil; [3]Adjunct Professor of the Department of Nutrition at the Universidade Federal de Pernambuco, Brazil; [4] Associate Professor of the Department of Tropical Medicine at the Universidade Federal de Pernambuco, Brazil; [5] Full Professor of the Department of Nutrition at the Universidade Federal de Pernambuco, Brazil

[CA] **(Corresponding author):** Prof. Ilma Kruze Grande de Arruda; Rua Manoel de Almeida Belo, 523 – Bairro Novo, Olinda/ CEP: 53030-030, Recife Pernambuco, Brazil.

<u>Phone:</u> +55- 81-999736122 **<u>E-mail:</u>** ilmakruze@hotmail.com

ABSTRACT

Background: Fat-soluble vitamin deficiency may be a health problem not recognized in children and adolescents. Objective: Estimate the prevalence and factors associated with the deficiency of vitamins A, D and E among adolescent students from Northeastern Brazil. Design: Transversal study with adolescents from 12 to 19 years old from both genders. A questionnaire to collect socioeconomic and lifestyle data and food intake was applied to adolescents. Then, an anthropometric evaluation and a blood sampling were performed to analyze serum concentrations of retinol, β-carotene, α-tocopherol and 25-hydroxy vitamin D (25(OH)D). Results: The inadequate intake of vitamins A (50.3%), E (94.0%) and D (99.8%), as well as α-tocopherol (88.1%), β-carotene (74.1%), 25(OH)D (50.9%) and retinol (46.6%) serum levels, were mostly deficient/insufficient. An increased risk of α-tocopherol deficiency was observed in girls (PR=1.11) and an increased risk of 25(OH)D deficiency was observed in boys (PR=1.41). An increased likelihood of β-carotene (PR=1.14) and 25(OH)D (PR=1.38) was observed in overweight individuals. Conclusions: The adolescents had a deficit in the intake and in serum levels of fat-soluble vitamins. The greatest risk of inadequacy was associated with gender and weight excess. However, the behavior of fat-soluble vitamins in adolescents needs further research.

Keywords: fat-soluble vitamins, adolescents, nutritional status, dietary intake, lifestyle

INTRODUCTION

Adolescence is a nutritionally vulnerable period for many reasons, especially by increased needs due to growth and development, and changes in dietary patterns and behaviors related to lifestyle[1]. Poor eating habits are considered a major public health problem because of its relation to the manifestation of chronic diseases. Among children and adolescents, this problem is more serious because many erroneous food preferences are established during this period [2].

The eating habits of Brazilian adolescents have been characterized as inadequate due to a high consumption of processed foods, rich in saturated fats, added sugar and sodium, combined with a low consumption of fruits, vegetables, beans and dairy products[3]. Consequently, there are increasing evidences linking micronutrient deficiencies to chronic diseases such as cardiovascular disease, cancer, diabetes and osteoporosis in adulthood [4,5].

Fat-soluble vitamins, because they are specifically involved in various cellular and tissue processes[6], increases their recommendations gradually during the fast growth period in puberty[7]. Poor nutritional intake could negatively interfere at this stage and increase the susceptibility of the young to developing several health problems.

The deficiency in fat-soluble vitamins may be a health problem not recognized in children and adolescents because these population groups are not routinely investigated[8], making the data on the status of these vitamins in adolescents scarce, especially in northeastern Brazil. Thus, this study aims to estimate the prevalence and the factors associated with the deficiency of vitamins A, D and E among adolescent students from northeastern Brazil.

METHODOLOGY

Study design and samples

Cross-sectional study involving adolescents from 12 to 19 years old from both genders, from March to April 2013, in a prospective cohort study conducted in 2007-2013 with teenagers recruited randomly by a multi-stage sampling process in public schools of Recife, northeastern Brazil. Adolescents who used pharmacological vitamin A, D, E or multivitamins in the last three months were excluded.

The sample size was based on an estimated prevalence (p) of α-tocopherol deficiency of 25%, a sampling error (d) of 5.5%, a confidence level of 95% (z) and an effect of design (c) of 2.1, considering that the sample selection was made by conglomerates. Using the formula $n = (z^2 \times p \times q \times c)/d^2$, corrected for a finite population, it resulted in a minimum sample of 370 individuals. To correct possible losses, a percentage of 11% [100/(100-11)] was increased, resulting in a sample with 416 adolescents. The final working sample was 411 adolescent students.

Methods and evaluation techniques

Data collection was conducted by applying a questionnaire addressing socioeconomic variables, lifestyle and the food intake of adolescents. The interviews aiming to obtain dietary data were performed by two experts and a Nutrition graduate student at the Universidade Federal de Pernambuco. To ensure the accuracy and reliability of the data, all members of the research team received training and orientation on the procedures and the routine development of the study. Then, an anthropometric evaluation and a blood sampling were performed to analyze serum concentrations of retinol, β-carotene, α-tocopherol and 25-hydroxy vitamin D (25(OH)D).

Socioeconomic status

The variables were obtained through interviews conducted at school and/or domicile, including questions about gender, age and socioeconomic classification. To determine the socioeconomic status (SES), the “Brazilian Economic Classification Criteria ", established by ABEP[9] was employed. This instrument uses a point scale, obtained by adding the possession of household items and the degree of the head of household educational level, which classifies the population in the following economic classes: A1, A2, B1, B2, C1, C2, D, and E, in descending order, respectively initiated by the highest purchasing income. Thus, SES was classified according to the following scheme: high SES (classes A1, A2), middle SES (classes B1, B2), low SES (classes C1, C2) and lowest SES (classes D, E).

Variables related to lifestyle

The adolescents were classified according to physical activity level into little active/sedentary or sufficiently active, according to the criteria proposed by Pate et al[10]. Adolescents were classified as smoker by reporting smoking an amount equal to or higher than five cigarettes/day[11]. Adolescents who declared drinking an amount of alcohol >30 g/day for males and >15 g/day for females were considered as positive to alcohol intake habit[12].

Dietary variables

Dietary intake was assessed by a semi-quantitative food frequency questionnaire for adolescents (FFQA), developed and validated by Slater et al. [13] and adapted for the usual food consumed in the area. The dietary intake was analyzed by the software DietSys, version 4.01 (National Cancer Institute, Bethesda, MD, USA), which uses as database the Chemical Composition Table of the United States Department of Agriculture (USDA). The results from the intake of vitamins A, D and E were compared with the values of *Dietary Reference Intakes* (DRI) proposed by the Institute of Medicine[14].

Anthropometric variables

The anthropometric evaluation consisted of a double measurement of weight and height. The average resulting from the two measurements was used as the final result. For data consistency, the measurements that had differences of more than 100 g for weight and 0.5 cm for height were not considered. Weight and height measurements were performed according to the original technique recommended by Lohman et al.[15]. The nutritional diagnosis of adolescents was defined based on BMI (body mass index) curves for age and gender according to the WHO reference data[16].

Biochemical variables

Biochemical analyses were performed after collecting approximately 10 mL of blood by venipuncture at school or domicile after a 10-12-hour fasting. The flasks were packed in Styrofoam boxes containing recyclable ice, sealed and transported for sample processing at the LAPAC laboratory of clinical analysis within a maximum of 2 hours. The serum was separated from erythrocytes by centrifugation and stored in two 2 mL tubes. Immediately, one of the serum aliquots was used to analyze the concentration of 25(OH)D. Another serum aliquot (2 mL) was frozen and later sent to the Centre for Micronutrients Research (CIMICRON) of the Federal University of Paraíba (UFPB) to determine serum retinol, β-carotene and α-tocopherol concentrations.

Retinol, β-carotene and α-tocopherol

The quantification of serum retinol, β-carotene and α-tocopherol levels followed the technical procedure described by Erhardt et al.[17]. The cutoff points recommended by the WHO for retinol levels were used, adopting the classification: poor: <0.35 μmol/L; low: 0.35-0.69 μmol/L; acceptable: 0.70-1.04 μmol/L; and normal: ≥ 1.05 μmol/L. Vitamin A deficiency was present when retinol levels were below 0.70 μmol/L. For α-tocopherol, the values ≥ 12 μmol/L were used as reference, while the values of β-carotene were considered appropriate in concentrations > 0.9 μmol/L.

25-hydroxyvitamin D

25(OH)D levels were measured by high-performance liquid chromatography (HPLC). There is a vitamin D deficiency when the value of 25(OH)D is less than 52.5 nmol/L and insufficient when values are between 52.5 and 72.4 nmol/L.

Data analysis

Data were double entered and verified with VALIDATE, a module of the Epi-Info software, version 6.0 (WHO/CDC, Atlanta, GE), to verify the consistency of the typing process. The statistical analysis was performed using the *Statistical Package for Social Sciences - SPSS*, version 13.0 (SPSS Inc., Chicago, IL).

Continuous variables were tested for distribution normality by the Kolmogorov-Smirnov test (to evaluate the symmetry of the distribution curve of variables). Data from normally distributed variables were expressed as means and standard deviation. The variables with a non-Gaussian distribution were presented as medians and the respective interquartile intervals. In the description of proportions, the binomial distribution was approximated to the normal distribution with a 95% confidence interval.

In the univariate analysis, the strength of association was assessed by prevalence ratios, the respective confidence intervals and the Pearson's chi square test. For the comparison among continuous data from independent samples, the "t" test or its nonparametric equivalent, Mann Whitney U test, was used. In all statistical analyses, a 5% significance level was used to reject the null hypothesis.

Ethical aspects

The study was approved by the Ethics Committee in Research with Human Beings of the Hospital Universitário Lauro Wanderley at Universidade Federal da Paraíba, Brazil (registration CEP/HULW no. 723/10), guided by ethical standards for research involving humans beings as determined by the resolution no. 196/96 of the National Health Council.

Adolescents and their parents were previously informed of the research objectives and the adopted methods. With its consent, the person responsible signed an informed consent form. It was guaranteed to adolescents and their parents, in addition to the confidentiality of data, the return of the results of evaluations. The researchers were available for any questions regarding procedures, risks, benefits and other questions related to the study.

RESULTS

The study included 411 adolescents. However, there were some losses in the following variables: socioeconomic status (53) and smoking (1) due to lack of answers, BMI/Age (3) due to inconsistencies between the two measurements, vitamin A (11) and E (11) intake due to information inconsistencies, serum retinol (14), β-carotene (87) and α-tocopherol (11) due to biological material insufficiency.

Most adolescents studied were females (61.1%; $CI_{95\%}$ 56.1-65.8). They had a median age of 15 years (IQ: 14-16 years) and a minimal variation of 12 and a maximum of 19 years. According to the socioeconomic status, it was observed that a higher percentage (41.6%; $CI_{95\%}$ 36.4-46.5) of the adolescents were in the socioeconomic class C. In relation to lifestyle, only 1.9% ($CI_{95\%}$ 0.8-3.8) of the adolescents mentioned the a smoking habit and 10.2% ($CI_{95\%}$ 7.4-13.5) were alcoholic. Regarding nutritional status, it was observed that most adolescents (69.3%; $CI_{95\%}$ 65.1-74.2) were normal (Table 1). In assessing food intake, it was observed that the fat-soluble vitamin intake among adolescents was mostly insufficient. With respect to serum levels, a high percentage of retinol (76.8%), β-carotene (74.1%), α-tocopherol (88.1%) and 25(OH)D (50.9%) deficiency/insufficiency was observed.

There was no significant difference between the consumption of vitamins A, D, E and β-carotene and serum levels of the respective fat-soluble vitamins, as shown in Table 2. However, children who ingested ≥ 10.42 mg/day of vitamin E had a significant decrease in serum concentrations of retinol and an increase in 25(OH)D (Table 2).

As shown in Table 3, it was observed that males had higher concentrations of retinol ($p=0.03$), α-tocopherol ($p=0.02$) and 25(OH)D ($p<0.001$). In relation to lifestyle, a significant increase in retinol was observed in adolescents who reported smoking ($p=0.03$) and higher concentrations of 25(OH)D ($p=0.02$) in individuals who drank alcoholic drinks. With regard to nutritional state, concentrations of retinol and α-tocopherol were significantly higher in overweight adolescents, while the serum levels of β-carotene and 25(OH)D decreased with an increased adiposity.

When factors associated with deficiency of fat-soluble vitamins were evaluated, it was found that the accumulation of body fat represented an increased risk of β-carotene (PR=1.14) and 25(OH)D (PR=1.38) insufficiency, while overweight exerted an opposite effect on alpha-tocopherol (Table 4). It was also noted that gender was a risk factor for the change in blood concentrations of vitamins, as female adolescents had a higher risk of lower values of α-tocopherol (PR=1.11), while boys had a higher risk of 25(OH)D (PR=1.41) inadequacy. Regarding 25(OH)D, it was observed that adolescents who did not smoke were more likely (PR=4.19) to reduce this vitamin in the bloodstream. No significant association between retinol inadequacy and the variables studied was found.

DISCUSSION

The deficit in the consumption of micronutrients is quite frequent among adolescents[18,19]. This has gained prominence after evidence demonstrated an association between the reduction in intake of some micronutrients, such as vitamins A, D, E, and an increased risk of diabetes, cardiovascular disease and cancer [20,21.]

In this sense, this study found quite alarming data, since more than 90% of adolescents had a low intake of vitamins D and E, while approximately 50% had an insufficient intake of vitamin A. These data follow the literature, since Peters et al.[22], revealed an inadequate vitamin D intake of around 85% among adolescents in the city of São Paulo, while Veiga et al.[23], in a national study, found that approximately 99% of individuals between 10 and 18 years had an inadequate intake of vitamin E. This is similar to the results obtained by Silva et al.[24], who, evaluating the intake of vitamin E of children and adolescents of a settlement in Maceió, found that the vitamin intake corresponded to 12% of daily needs. There are reports of deficient intake[19], optimal intake[25] and intake above the recommended for vitamin A[24].

Reduced levels of fat-soluble vitamins in the bloodstream were also prevalent in this study, since adolescents have an inadequacy in more than 70% of the levels of β-carotene and α-tocopherol, approximately 50% of insufficiency in concentrations of 25(OH)D and 32.1% deficiency in retinol levels. Despite few reports with samples involving adolescents, the literature shows that the levels of 25(OH)D are, in fact, highly insufficient/deficient[25], while retinol levels were insufficient in about 10-28% of adolescents [26,27], and the inadequacy of α-tocopherol is around 25% [28]. Although the literature demonstrates a relatively high frequency of these nutrients, this study showed higher values, reinforcing the importance of the development of more representative studies on populations in this age group.

In the sample studied, it was observed that boys had significantly higher values of retinol, α-tocopherol and 25(OH)D. Girls had a higher risk of deficiency of α-tocopherol, whereas boys had a higher risk of 25(OH)D inadequacy. This difference may be due to possible differences arising from the pubertal development of the genders. Hormonal factors might be responsible for these differences, since vitamins are highly active compounds associated with the activity of all regulatory chains of the gonadotropic pituitary function and participate in the synthesis of corticosteroids and sex hormones [29].

It is important to note that adolescents are a group vulnerable to fat-soluble vitamin deficiency, and poor eating habits could exacerbate this deficiency. However, in this study, there was no significant difference between the consumption of vitamins A, D, E and their respective serum concentrations, which leads us to infer that in addition to absolute values of consumed micronutrients, other factors could interfere with their blood concentrations.

The intake of vitamins below the recommended values for an extended period may be one of the main factors that could interfere with serum levels because the concentrations of fat-soluble vitamins remain consistent unless the individual consumes chronically inadequate amounts of these vitamins[30]. In addition, the bioavailability of vitamins may also influence serum levels since the absorption of fat-soluble vitamins depends on the lipid components involved in the formation of the micelle and in pancreatic and biliary stimulus. It also depends on diet composition: certain lipids and other nutrients may negatively interfere with the absorption of vitamins[31].

In this study, adolescents who consumed higher amounts of vitamin E had a significant decrease in serum retinol concentrations, possibly because a high amount of vitamin E may inhibit the absorption of β-carotene or its conversion into retinol in the intestine [32]. It was also noted that a higher intake of vitamin E seems to positively affect the increase of 25(OH)D. However, there are no reports elucidating this finding, which leads us to infer that similarly to the interaction between vitamin A and the iron metabolism, which until recently was a not known association, vitamin E intake could positively affect the bioavailability of vitamin D. However, more studies are needed to evaluate and clarify the probable mechanism of interaction between these two vitamins. In addition, it is suggested that in evaluating the consumption of fat-soluble vitamins, the factors that may interfere in the bioavailability of these micronutrients be considered. Suarez and Schramm-Sapyta[33] report that in order to identify the deficiency of fat-soluble vitamins, it is important not to evaluate food consumption alone, since the dietary intake seems to be a reliable measurement for evaluating circulating levels of these vitamins.

In this study, besides a high inadequacy in the status of fat-soluble vitamins, it was observed that approximately 27.9% of adolescents were overweight. These values are higher than the values obtained by Leal et al.[34] in the *III State Research on Health and Nutrition* (PESN) in 2006. It was found that 13.3% of the adolescents from the Pernambuco state, northeastern Brazil, were overweight. Other studies in Brazilian northeastern cities showed a lower prevalence of overweight in adolescents when compared to the prevalence found in the present study, with estimates ranging from 14.3% to 20.8% [35,36]. These data demonstrate a tendency in the increasing prevalence of overweight and obesity among adolescents in the evaluated region.

There are several factors that may influence the excessive weight gain in adolescents, such as socioeconomic level, maternal education, early sexual maturation, insufficient levels of physical activity and inadequate food intake [34-36]. Among these factors, diet seems to play a key role in obesity, because it is common to adolescents not to have breakfast and consume high-calorie foods, rich in sugars and fats, and reduction in the intake of fruits/vegetables[37].

Studies demonstrated an inverse association between concentrations of fat-soluble vitamins and overweight in children and adolescents from both genders[38,39]. Evidence suggests that a decrease in the concentration of fat-soluble vitamins in the plasma may occur in obesity due to a lower intake of these nutrients and/or to a greater deposition in the adipose tissue.

By being soluble in fats, they are deposited in adipocytes and thus decrease bioavailability in individuals with adiposity excess [40]. Thus, a higher adiposity is associated with increased levels of free radicals, leading to the reduction of the concentrations of antioxidant liposoluble vitamins in an attempt to reduce the oxidative stress resulting from overweight[41].

However, this study found that overweight adolescents had an increase in the concentrations of retinol and α-tocopherol and a decrease of β-carotene and 25(OH)D concentrations when compared to individuals with a normal weight. These findings differ from the literature, since there are reports of a decrease of vitamins D, E and β-carotene in the bloodstream in overweight individuals [42,43], whereas retinol presents conflicting data, since some authors have reported an increase in this vitamin with an increase in adiposity [42] and others show no association between retinol and obesity [27].

These differences could be attributed to the storage locations of fat-soluble vitamins in the human body, for about 80-90% of the retinol is stored in the liver, while carotenoids and vitamins D and E are ideally stored in the adipose tissue [45]. That is, the concentration of retinol would depend primarily on liver reserves and would exert less influence to fluctuations of adipose tissue.

A possible explanation is that, due to the inflammatory process resulting from overweight, there would initially be a greater recruitment of antioxidant vitamins (A, E and carotenoids) in an attempt to neutralize the free radicals produced, thus increasing their concentration in the bloodstream. β-carotene, as well as having an antioxidant function and the possibility of being diverted for conversion to vitamin A in the liver, would likely decrease its concentrations. Another factor that could influence the decrease in the concentration of these vitamins would be the intensity and the duration of the inflammatory process. However, as this study did not use biochemical markers, it prevented us from confirming the degree of inflammation that adolescents have.

Regarding vitamin D, the reduced values in obese individuals could be due to a higher deposition in adipocytes and a lower recruitment of this vitamin, since this nutrient does not have an antioxidant activity. It has been speculated that a deficiency of this vitamin could trigger the accumulation of body fat, because, with the deposit of vitamin D in adipocytes, its lower bioavailability would trigger a cascade of reactions by the hypothalamus, which would result in an increased hunger feeling and a reduced expenditure of energy[46]. In addition, a decrease in vitamin D levels would increase the parathyroid hormone, which in turn would cause an elevation in intracellular calcium levels in adipocytes, which could act on the increased expression of fatty acid synthase, a key enzyme to the regulation of lipid deposition as well as to the reduction of lipolysis[47].

Upon evaluating the concentration of fat-soluble vitamins according to gender (data not shown), boys showed an increase in the concentrations of retinol and α-tocopherol and a reduction of β-carotene and 25(OH)D concentrations as adiposity increased. In girls, only α-tocopherol was high with overweight. As previously mentioned, these variations may be caused by hormonal influences on the weight development process, but they may also be due to differences existing in different body fat deposition areas. Women deposit more fat in the femoral and gluteal region, and men deposit more fat in the central region, which configures a less inflammatory profile for females[48]. Thus, the mobilization of vitamins to the bloodstream would be less intense in girls compared to boys with an increase in adiposity.

The lower concentration of β-carotene observed in adolescents from a higher socioeconomic level shows that purchasing power may interfere with diet choices, because, as the β-carotene is considered a relevant indicator of fruit and vegetable intake[28], adolescents would possibly show a reduced consumption of these foods. This is because, unlike retinol, in which blood levels are more stable and maintained because of deposits, β-carotene concentrations are more variable, probably because of fluctuations in the carotenoid intake [49].

Regarding the variable life style, adolescents who reported smoking had higher concentrations of retinol, and those who did not smoke had a higher risk of insufficiency 25(OH)D levels. However, it should be noted that the sample of smoker adolescents was very small (n=8), which shows the need for further research to investigate whether this association is true or if it was just one confounding factor of this study.

This study also found that adolescents who drank alcohol had lower serum concentrations of vitamin D. This could be due to the relation between alcohol and food consumption, as individuals who drink alcohol are also predisposed to an eating binge because alcohol may amplify the individual's perception of appetite in response to food stimuli[50], and thus could favor a greater consumption of food and a consequent higher intake of fat-soluble vitamins. Possibly only the chronic alcohol consumption would be associated with a decrease in the concentrations of both fat-soluble and water-soluble vitamins.

With regard to the limitations of the study, because it was a cross-sectional study, it was not possible to guarantee causal relations, and confounding variables may have affected the reported associations. In addition, biochemical markers monitoring the presence and intensity of oxidative stress were not used, which prevented us from evaluating the changes in concentrations of vitamins related to the inflammatory process in the presence of overweight/obesity.

Evaluated adolescents have a potential risk of inadequacy of fat-soluble vitamins, with a significant deficit both in consumption and serum levels. Although factors such as gender and overweight interfere with serum concentrations, the metabolic behavior of vitamins A, D, E and β-carotene appears to differ according to different situations. Thus, it is necessary to understand the biochemical pathways that each vitamin takes, particularly with respect to increased adiposity, especially because it is one of the most prevalent nutritional disorders among adolescents, and liposoluble vitamins appear to be negatively related to excess of weight.

These findings point to the fact that the consumption of vitamin E appears to influence the metabolism and bioavailability of vitamin D, but more studies are needed to elucidate this association. This study demonstrates that the behavior of vitamins A, D and E in adolescents needs more research in order to identify the status of these nutrients in this population group, so that specialized and focused strategies to reduce these deficiencies are adequately prepared.

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Table 1. Characteristics of adolescent students from Recife, northeastern Brazil, 2013.

Variables	n	%	CI $_{95\%}$
Gender			
Boys	160	38,9	34,1-43,8
Girls	251	61,1	56,1-65,8
Socioeconomic status			
A+B	97	27,5	22,88-32,45
C	147	41,6	36,45-46,48
D+E	109	30,9	26,09-35,98
Tabagism			
Yes	8	1,9	0,8-3,8
No	402	97,8	96,1-99,1
Alcoholic			
Yes	42	10,2	7,4-13,5
No	369	89,8	86,4-92,5
Physical activity			
Yes	259	63	58,1-67,6
No	152	37	32,3-41,8
Nutritional status			
Low weight	9	2,2	1,0-4,1
Eutrophic	285	69,3	65,1-74,2
Overweight	71	17,3	13,8-21,4
Obesity	43	10,5	7,7-13,9
Food intake			
Vitamin A			
Adequate	199	49,8	44,7-54,7
Inadequate	201	50,3	45,2-55,2
Vitamina E			
Adequate	24	6,0	3,9-8,8
Inadequate	376	94,0	91,2-96,1
Vitamina D			
Adequate	1	0,2	0,0-1,3
Inadequate	410	99,8	98,8-99,9
Serum concentrations			
Retinol			
Adequate	92	23,2	19,1-27,6
Mild deficiency	176	44,3	39,3-49,3
Moderate deficiency	101	25,4	21,2-30,0
Severe deficiency	28	7,1	4,7-9,8
β-carotene			
Adequate	84	25,9	21,2-31,0
Deficiency	240	74,1	68,9-78,7
α-tocopherol			
Adequate	47	11,9	8,9-15,5
Deficiency	347	88,1	84,4-91,1
25(OH)D			
Adequate	202	49,1	44,2-54,1
Insufficient	189	46,0	41,1-50,9
Deficiency	20	4,9	2,9-7,4

BMI – body mass index; WC: waist circumference; CI – Confidence Interval; 25(OH)D: 25 Hydroxy-vitamin D; Criteria of socieconomic status classification-2013: descending order (being A the household with the highest purchasing power); Adequate Retinol >0,7 µmol/L, Adequate β-caroteno: >0,9 µmol/L; Adequate α-tocoferol > 12 µmol/L; Adequate 25(OH)D: >72,4 nmol/L. Adequate food intake: vitamina A > 900mcg/day; vitamina E > 15 mg/day; vitamina D > 15mcg/day. Losts: BMI/Age by inconsistances between the two measurements, food intake of vitamin A and E for inconsistencies informations, serum retinol , β-carotene and α-tocopherol by biological material failure

Table 2. Association between dietary intake and serum concentrations of fat-soluble vitamins of adolescent students, northeastern Brazil, 2013.

	Concentrações séricas											
		Retinol (μmol/L)			β-carotene (μmol/L)			α-tocopherol (μmol/L)			25 Hydroxy-vitamin D (nmol/L)	
Food intake	*n*	Median ± SD	*p**	*n*	Median(QI)	*p***	*n*	Median (QI)	*P***	*n*	Median(QI)	*p***
vitamin A												
≤461,28 mg	97	0,85±0,36	0,64	81	0,8972(0,8968-0,8993)	0,31	97	7,42(5,91-8,52)	0,37	100	71,16(56,95-86,87)	0,26
≥ 2249,44 mg	96	0,83±0,36		79	0,8976(0,8969-0,9001)		94	6,71(5,05-8,47)		100	75,66(61,23-93,70)	
β-carotene												
≤602,08 mg	96	0,86±0,36	0,77	77	0,8972(0,8967-0,8993)	0,23	96	7,11(5,56-8,43)	0,63	100	71,16(57,51-86,87)	0,24
≥ 2399,02 mg	97	0,84±0,37		76	0,8977(0,8969-0,9095)		95	6,78(5,11-8,56)		100	75,29(61,28-93,70)	
vitamin E												
≤5,71 mg	94	0,88±0,36	0,04	82	0,8977(0,8969-0,9163)	0,71	93	6,98(4,99-8,34)	0,43	97	71,84(56,68-86,63)	0,02
≥ 10,42 mg	98	0,77±0,34		78	0,8976(0,8969-0,8994)		96	6,38(4,68-7,74)		100	75,49(63,05-98,83)	
vitamin D												
≤1,31 mcg	97	0,82±0,28	0,45	80	0,8976(0,8969-0,9043)	0,32	96	6,78(4,88-8,17)	0,58	99	70,95(60,11-82,42)	0,52
≥ 3,86 mcg	99	0,85±0,38		78	0,8971(0,8967-0,8994)		97	6,78(4,99-8,89)		103	71,84(58,34-88,63)	

* Student's t Test unpaired; ** U test of Mann-Whitney. Food intake – used comparison between first and last quatils

Table 3. Serum concentrations of retinol, β-carotene, α-tocopherol and 25-hydroxy vitamin D according to lifestyle and nutritional status of adolescent students from Recife, northeastern Brazil, in 2013.

		Retinol (μmol/L)			α-tocopherol (μmol/L)			β-carotene (μmol/L)			25 Hydroxy-vitamin D (nmol/L)	
	n	Median ± SD	*p**	*n*	Median (QI)	*p***	*n*	Median (QI)	*p***	*n*	Median (QI)	*p***
Age (years)												
12-15	271	0,86±0,36	0,14	269	7,06(5,12-8,63)	0,31	227	0,8974(0,8968-0,8998)	0,62	285	72,49(60,21-87,52)	0,29
16-19	126	0,80±0,28		125	6,71(5,37-7,90)		97	0,8977(0,8968-0,9053)		126	69,72(58,65-87,72)	
Gender												
Boys	155	0,88±0,33	0,03	153	7,11(5,86-9,62)	0,02	122	0,8973(0,8967-0,9053)	0,18	160	76,91(62,76-98,13)	<0,001
Girls	242	0,81±0,34		241	6,78(4,86-8,23)		202	0,8977(0,8969-0,9005)		251	67,63(57,67-82,21)	
Socioeconomic status												
A+B	95	0,83±0,34	0,51†	95	6,81(4,32-8,48)	0,49#	75	0,8973(0,8967-0,8996)	<0,001#	97	71,37(59,67-91,83)	0,12#
C	139	0,84±0,35		137	7,03(4,99-8,76)		112	0,8977(0,8968-0,9022)		147	71,84(60,11-86,37)	
D+E	106	0,79±0,30		106	6,94(5,72-8,26)		89	0,8974(0,8968-0,8988)		109	72,28(60,67-86,20)	
Smoking												
Yes	8	0,98±0,47	0,03	8	7,59(6,24-9,29)	0,42	5	0,9025(0,8968-0,9276)	0,63	8	90,59(77,86-109,53)	0,06
No	389	0,84±0,34		388	6.86(5,14-8,56)		319	0,8975(0,8968-0,9004)		403	71,84(60,11-87,07)	
Alcoholic												
Yes	42	0,83±0,35	0,84	42	6,62(5,11-8,29)	0,53	35	0,8974(0,8966-0,9025)	0,29	42	82,99(65,36-104,91)	0,02
No	355	0,84±0,34		352	6.91(5,17-8,59)		289	0,8975(0,8968-0,9008)		369	70,95(59,89-86,75)	
Physical activity												
Yes	253	0,84±0,33	0,11	251	6,96(5,26-8,86)	0,12	206	0,8973(0,8967-0,8998)	0,109	259	72,49(60,32-89,28)	0,31
No	144	0,83±0,35		143	6,78(4,88-7,99)		118	0,8977(0,8969-0,9016)		152	69,39(58,39-86,81)	
BMI/Age												
Weight excess	113	0,91±0,38	0,01	111	7,44(6,33-9,45)	<0,001	96	0,8970(0,8967-0,8979)	0,001	114	67,18 (57,46-81,39)	0,01
No weight excess	282	0,81±0,32		281	6,62(4,84-8,29)		226	0,8978(0,8969-0,9101)		294	73,54(61,17-89,67)	

* Student's t Test unpaired; ** Teste U de Mann-Whitney; † ANOVA. # Kruskall-Williams.

BMI – body mass index; Criteria of socieconomic status classification-2013: descending order (being A the household with the highest purchasing power)

Table 4. Factors associated with inadequate serum retinol, α-tocopherol, β-carotene and 25-hydroxy vitamin D of adolescent students from Recife, northeastern Brazil, 2013.

Variables	Retinol (µmol/L)					α-tocopherol (µmol/L)					β-carotene (µmol/L)					25 Hydroxy-vitamin D (nmol/L)				
		Insufficient					Insufficient					Insufficient					Insufficient			
	N	n	%	PR ($CI_{95\%}$)	p*	N	n	%	PR ($CI_{95\%}$)	p*	N	n	%	PR ($CI_{95\%}$)	p*	N	n	%	PR ($CI_{95\%}$)	p*
Age(years)																				
12-15	268	86	32,1	1,00 (0,7-1,4)	0,98	269	235	87,4	1,00		227	172	75,8	1,08(0,9-1,2)	0,35	285	144	50,5	1,00	
16-19	122	39	32,0	1,00		125	112	89,6	1,03(0,9-1,1)	0,63	97	68	70,1	1,00		126	68	54,0	1,07(0,9-1,3)	0,59
Gender																				
Boys	153	44	28,8	1,00(0,9-1,6)	0,31	153	126	82,4	1,00		122	89	73,0	1,00		251	146	58,2	1,41(1,1-1,7)	0,001
Girls	237	81	34,2	1,19		237	221	91,7	1,11(1,03-1,2)	0,01	202	151	74,8	1,02(0,9-1,2)	0,82	160	66	41,3	1,00	
SES					0,67**					0,20**					0,21**					0,94**
D+E	104	35	33,7	1,11(0,8-1,6)	0,69	95	79	83,2	1,00		75	58	77,3	1,06(0.9-1,3)	0,39	109	56	51,4	1,00	
C	135	41	30,4	1,00		137	119	86,9	1,04(0,9-1,2)	0,55	112	79	70,5	1,00		147	76	51,7	1,01(0,8-1,3)	0,94
A+B	95	34	35,8	1,18(0,8-1,7)	0,47	106	97	91,5	1,10(0,9-1,2)	0,11	89	72	80,9	1,15(0,9-1,3)	0,13	97	52	53,6	1,04(0,8-1,3)	0,86
Tabagism																				
Yes	8	1	12,5	1,00		8	7	87,5	1,00		5	2	40,0	1,00		8	1	12,5	1,00	
No	382	124	32,5	2,60(0,4-16,3)	0,45#	386	340	88,1	1,01(0,8-1,3)	1,00#	319	238	74,6	1,87(0,6-5,5)	0,11	403	211	52,4	4,19(0,7-26,3)	0,03#
Alcoholic																				
Yes	41	13	31,7	1,00		42	39	92,9	1,06(0,9-1,2)	0,45	35	26	74,3	1,00(0,8-1,2)	0,86	42	16	38,1	1,00	
No	349	112	32,1	1,01(0,6-1,6)	0,89	352	308	87,5	1,00		289	214	74,0	1,00		369	196	53,1	1,39(0,9-2,1)	0,09
Physical activity																				
No	141	43	30,5	1,00		143	128	89,5	1,03(0,9-1,1)	0,61	118	84	71,2	1,00		152	82	53,9	1,07(0,9-1,3)	0,52
Yes	249	82	32,9	1,08 (0,8-1,5)	0,70	251	219	87,3	1,00		206	156	75,7	1,06(0.9-1,2)	0,44	259	130	50,2	1,00	
BMI/Age																				
Weight excess	109	31	28,4	1,00		111	89	80,2	1,00		96	84	87,5	1,14(1,1-1,4)	<0,001	114	68	59,6	1,38(1,1-1,7)	0,005
No weight excess	279	93	33,3	1,17 (0,8-1,6)	0,42	281	256	91,1	1,14 (1,0-1,3)	0,005	226	154	68,1	1,00		294	114	49,0	1,00	

*Chi-square test; **ANOVA; #Fisher's Exact Test;

SES: Socioeconomic Status; BMI: body mass index; PR: prevalence ratio; CI: confidance interval; QI: quartile interval; Criteria of socieconomic status classification-2013: descending order (being A the household with the highest purchasing power.); Adequate Retinol >0,7 µmol/L, Adequate β-caroteno: >0,9 µmol/L; Adequate α-tocoferol > 12 µmol/L; Adequate 25(OH)D: >72,4 nmol/L.

7.2 Artigo 2

Tittle **Adiposity, Inflammation And Fat-Soluble Vitamins In Adolescents**

Authors: Rebecca Peixoto Paes-Silva[1], Patrícia Calado Ferreira Pinheiro Gadelha[1] Regiane Maio[2], Célia Maria Machado Barbosa de Castro[3], Ilma Kruze Grande de Arruda[4], Alcides da Silva Diniz[4]

Affiliation: [1]Doctorate Student in Nutrition at the Universidade Federal de Pernambuco, Brazil; [2]Adjunct Professor of the Department of Nutrition at the Universidade Federal de Pernambuco, Brazil; [3] Associate Professor of the Department of Tropical Medicine at the Universidade Federal de Pernambuco, Brazil; [4] Full Professor of the Department of Nutrition at the Universidade Federal de Pernambuco, Brazil

[CA] **(Corresponding author):** Prof. Ilma Kruze Grande de Arruda; Rua Manoel de Almeida Belo, 523 – Bairro Novo, Olinda/ CEP: 53030-030, Recife Pernambuco, Brazil.

Phone: +55- 81-999736122 **E-mail:** ilmakruze@hotmail.com

ABSTRACT

Objective: Evaluate the association between inflammatory process, adiposity and vitamins A, D and E in adolescents. **Methods:** Transversal study with adolescents from 12 to 19 years old from both genders. A questionnaire to collect social and economic data, lifestyle and food intake of adolescents was used. Then, an anthropometric evaluation and a blood sampling were performed to analyze serum concentrations of α-1-acid glycoprotein (AGA), retinol, β-carotene, α-tocopherol and 25-hydroxy vitamin D (25(OH)D). **Results:** The levels of AGA were higher for abdominal obesity in both genders. Male adolescents with insufficient α-tocopherol serum levels had low levels of AGA ($p=0.03$) and an increased risk of 25(OH)D and β-carotene deficiency regarding total and abdominal fat; girls had an increased risk of insufficient β-carotene with abdominal obesity. **Conclusion:** Abdominal adiposity reflects a higher risk of inflammation and causes different changes to the concentration of fat-soluble vitamins according to gender.

Keywords: Inflammation, Adolescents, Fat-soluble vitamins, Obesity, Food intake.

INTRODUCTION

Obesity has been considered as the most important nutritional disorder [1]. It is considered the global epidemic of the XXI century due to its high prevalence among children, adolescents and young adults over the past 30 years [2]. Weight excess is implicated in a wide variety of health problems arising from the increase in the proportion of body fat and disorders associated with the increase in mechanical load of the adipose tissue [3].

After discovering that many substances are secreted by adipocytes, such as hormones and cytokines, the inflammatory and endocrine functions of the adipose tissue were then demonstrated [4,5] . Studies have shown that the inflammatory reaction may be a common factor among metabolic diseases, forming a link between adiposity, metabolic syndrome and cardiovascular diseases [6,7].

Evidence suggests that a decrease in the concentration of fat-soluble vitamins in the plasma may occur in obesity due to a lower intake of these nutrients and/or a greater deposition in the adipose tissue. By being soluble in fats, they are deposited in adipocytes and thus decrease bioavailability in individuals with adiposity excess [8]. Furthermore, vitamin carrier proteins behave as negative proteins of the acute phase of inflammation [9], thus reducing its availability in the plasma during a chronic inflammation that derives from obesity.

It has been observed that obese children and adolescents are at an increased risk of low levels of fat-soluble vitamins compared to children and adolescents with a normal weight [10,11]. Considering that the current nutritional recommendations do not take into account the bioavailability of fat-soluble vitamins in the presence of a metabolic inflammation associated with obesity, a chronic state of inadequacy of these micronutrients may cause a greater risk of nutritional disorders in overweight adolescents [12]. Thus, this study aims to evaluate the association between inflammation, adiposity and vitamins A, D and E in adolescents.

METHODOLOGY

Study design and samples

Cross-sectional study involving adolescents from 12 to 19 years old from both genders, from March to April 2013, in a prospective cohort study conducted in 2007-2013 with teenagers recruited randomly by a multi-stage sampling process in public schools of Recife, northeastern Brazil. Adolescents who used pharmacological vitamin A, D, E or multivitamins in the last three months were excluded.

The sample size was based on an estimated prevalence (p) of α-tocopherol deficiency of 25%, a sampling error (d) of 5.5%, a confidence level of 95% (z) and an effect of design (c) of 2.1, considering that the sample selection was made by conglomerates. Using the formula $n = (z^2 \times p \times q \times c)/d^2$, corrected for a finite population, it resulted in a minimum sample of 370 individuals. To correct possible losses, a percentage of 11% [100/(100-11)] was added. The final working sample was 411 adolescent students.

Methods and evaluation techniques

The questionnaire concerning food intake, blood sampling and anthropometric measurements was applied by experts trained and oriented on the procedures and development routine of the study.

Dietary variables

The dietary intake was assessed by a semi-quantitative food frequency questionnaire for adolescents (FFQA) developed and validated by Slater et al[13], adapted for the usual food consumed in the study area. The analysis was performed using the DietSys software, version 4.01 (National Cancer Institute, Bethesda, MD, USA). The results from the intake of vitamins A, D and E were compared with the values of the *Dietary Reference Intakes* (DRI) proposed by the Institute of Medicine [14].

Anthropometric variables

Weight and height measurements were performed according to the original technique recommended by Lohman et al [15]. The WC (waist circumference) was obtained at the midpoint between the last rib and the iliac crest with a flexible and inelastic tape measure without compressing tissues [16]. The nutritional diagnosis of adolescents was defined according to the BMI (body mass index) curves established by the WHO [17]. In the diagnosis of abdominal obesity, the cutoff point for WC classification was established by Taylor et al [16] and the WHtR (*waist*-to-height ratio) was recommended by Li et al [18].

Biochemical variables

Biochemical analyses were performed after collecting 10 mL of blood after a 10 to 12-hour fasting. The flasks were packed and transported for sample processing at the LAPAC clinical analysis laboratory, where the concentrations of α-1-acid glycoprotein and 25-hydroxy vitamin D (25(OH)D) were analyzed. A serum aliquot (2 mL) was frozen and later sent to the Centre for Micronutrients Research (CIMICRON) of the Federal University of Paraíba (UFPB) to determine retinol, β-carotene and α-tocopherol serum concentrations.

α-1-acid glycoprotein

The α-1 acid glycoprotein (AGA) was quantified by immunoturbidimetry using Roche reagents, calibrators and controls in a Cobas Mira (Roche) automated system. There was inflammation if a value above 0.9 g/L was obtained.

Retinol, β-carotene and α-tocopherol

The quantification of retinol, β-carotene and α-tocopherol serum levels followed the technical procedure described by Erhardt et al. [19]. Cutoff points recommended by the WHO were used for retinol levels, considering retinol deficiency at <0.70 µmol/L. For α-tocopherol, it was used as reference ≥ 12 µmol/L [20]. The values of β-carotene were considered suitable at > 0.9 µmol/L [21].

25-hydroxy vitamin D

The 25(OH)D levels were measured by high-performance liquid chromatography (HPLC). The insufficiency of 25(OH) was defined as <72.4 nmol/L [22].

Data analysis

Data were double entered and verified with VALIDATE, a module of the software Epi-Info, version 6.0 (WHO/CDC, Atlanta, GE), to verify the consistency of the typing process. The statistical analysis was performed using the *Statistical Package for Social Sciences - SPSS*, version 13.0 (SPSS Inc., Chicago, IL).

Continuous variables were tested for distribution normality using the Kolmogorov-Smirnov test (to evaluate the symmetry of the distribution curve of variables). Data from normally distributed variables were expressed as means and standard deviation. The variables with a non-Gaussian distribution were presented as medians and the respective interquartile intervals. In the description of proportions, the binomial distribution was approximated to the normal distribution by a 95% confidence interval.

In the univariate analysis, the strength of association was assessed by prevalence ratios, the respective confidence intervals and the Pearson's chi square test. For the comparison among continuous data from independent samples, the "t" test or its nonparametric equivalent, Mann Whitney U test, was used. In all statistical analyses, a 5% significance level was used to reject the null hypothesis.

Ethical aspects

The study was approved by the Ethics Committee in Research with Human Beings of the University Hospital Lauro Wanderley at the Federal University of Paraíba (registration CEP/HULW no. 723/10), guided by ethical standards for research involving humans beings as determined by the resolution no. 196/96 of the National Health Council. Adolescents and their parents were previously informed of the research objectives and the adopted methods. With its consent, the person responsible signed an informed consent form.

RESULTS

The study included 411 adolescents with a median age of 15 years (IQ: 14-16 years). According to BMI/Age, it was observed that 27.9% individuals were had weight excess, being 17.4% (n=71) overweight and 10.5% (n=43) obese. Regarding abdominal fat, 16.8% and 14.4% had a high WC and WHtR, respectively. With regard to serum levels of fat-soluble vitamins, the majority had low concentrations of retinol, α-tocopherol, β-carotene and 25(OH)D. Inadequate values were also observed upon evaluating the dietary intake of vitamins A, D and E, as seen in Table 1.

Regarding the inflammatory process, AGA showed no change in serum levels with the increase of total adiposity, but was high for male adolescents classified with abdominal obesity according to the WC ($p=0.04$) and WHtR ($p=0.03$), while girls had increased concentrations only with a high WC ($p<0.01$) (Table 2). In relation to the concentrations of vitamins, AGA had a decrease in its levels in the presence of insufficient amounts of serum α-tocopherol in male adolescents ($p=0.03$). Regarding food intake, AGA did not show a significant difference when varying the consumption of fat-soluble vitamins.

Upon evaluating the concentration of fat-soluble vitamins according to nutritional status, it was found that boys showed an increase in retinol and α-tocopherol concentrations as adiposity increased, while the concentrations of β-carotene and 25(OH)D in blood decreased. In relation to girls, only α-tocopherol significantly increased its concentrations with a greater adiposity, as shown in Table 3. When the association between the type of adiposity and the concentrations of vitamins were evaluated, boys had a higher risk of 25(OH)D and β-carotene deficiency in total and abdominal adiposity. However, when there was no adiposity, they presented a risk of retinol and α-tocopherol deficit (Table 4). Girls, however, only demonstrated a risk of β-carotene deficiency when the WC (PR=1.33) and WHtR (PR=1.33) were high.

DISCUSSION

The high prevalence of overall adiposity among adolescents revealed in this study reflects the magnitude of the problem. It is observed, however, that by evaluating abdominal fat, the percentages are reduced to 16.8% according to WC and 14.4% according to WHtR compared to the diagnosis of total obesity. These are data similar to that found by Pinto et al. [23], who demonstrated a prevalence of abdominal obesity of 14.9% and 12.5% according to WC and WHtR, respectively, in adolescents at the same area of northeastern Brazil. In southern cities, higher frequencies were reported, varying between 28.7 and 30.8% of abdominal obesity among adolescents [24,25].

Regardless of the region, adolescents with a high body fat are more likely to accumulate intra-abdominal fat [26] and a consequent increase in WC. As the number of adipocytes is defined during childhood and adolescence and varies little during adulthood [27], the findings of this study demonstrate an increased risk of morbidity for these individuals, since, as in adults, an increased adiposity increases the risk of cardiovascular and metabolic complications [28].

Although body fat is related to certain metabolic complications, several consequences of obesity are more strongly associated with abdominal fat [29-31]. The amount of abdominal adipose tissue plays a key role, and perhaps induce the risk to the health of overweight and obese individuals [32]. Therefore, knowing that the accumulation of visceral fat has a better correlation of metabolic abnormalities than the amount of subcutaneous fat, it has been suggested that methods of central deposition evaluation of body fat be used to diagnose obesity in children and adolescents [29].

It is postulated that the obese individual has a persistent inflammation of the adipose tissue [28]. Proinflammatory cytokines associated with the accumulation of adipose tissue would explain the development of obesity-related diseases [33,34]. With the increase in the production of various adipokines, such as IL-6 and TNF-α, the insulin signaling pathway would be impaired, leading to one of the early complications of obesity: resistance to insulin. Depending on the intensity of this stimulus, the condition may worsen, triggering diabetes mellitus type 2 and other comorbidities [35].

In the association between inflammation and adiposity, it was observed that the AGA was increased in both genders only in the presence of abdominal obesity; an increase in total body fat was not observed. These findings differ from the literature, since there are reports of high AGA in overweight and obese adolescents according to BMI[36,37]. Alfadda et al. [38] observed that the mRNA expression of AGA would be correlated with the expression of TNF-α, IL-6 and adiponectin in the visceral adipose tissue, while in the subcutaneous adipose tissue, this expression is correlated only with TNF-α and adiponectin. This association may explain in part our findings, since the greatest inducer for raising the AGA would perhaps be inflammatory cytokines released by the visceral adipose tissue. In addition, when only the BMI is used to classify obesity, the diagnosis may be flawed, as it is not sensitive to predict whether the increase in body mass is an increased amount of muscle or fat, nor evidences the deposition area.

Studies also demonstrate that the concentrations of a wide range of vitamins and trace elements in plasma are changed in an inflammation regardless of tissue reserves [39,40]. Plasma concentrations of micronutrients are at least in part mediated by proinflammatory cytokines that suppress the hepatic production of many protein carriers, increase capillary permeability and promote the sequestration of some micronutrients to the liver and other organs [41]. The literature shows that retinol [42], vitamin E [43] and vitamin D [39] concentrations are significantly lower during an inflammation.

In this study, it was not possible to evaluate the concentration of vitamins according to the presence of an inflammatory process because none of the adolescents studied had inflammations according to the cutoff point established for AGA. However, it was observed that male adolescents with insufficient levels of α-tocopherol had the average serum concentrations of AGA reduced. According to reports cited above, an inverse relation between inflammation and α-tocopherol would be expected to be found. However, in study by Ulatowski et al. [44], the authors reported that oxidative stress might increase the gene expression of the transfer protein α-tocopherol (α-TTP), since, as this vitamin is the most important fat-soluble antioxidant, the distribution of vitamin E would prevent a further oxidative damage.

Regarding the variation of AGA concentrations and the intake of fat-soluble vitamins, this study did not observe any changes. Despite vitamins A, E and carotenoids exerting an antioxidant role, there are reports indicating that the intake of vitamin E and β-carotene is not a predictor of a subclinical inflammation in children and adolescents [45], and even a four-month supplementation with vitamin E has not proved to be effective in altering the inflammatory markers in overweight adolescents[36]. It is important to consider that the absorption, transport and distribution to tissues may interfere with the effectiveness of the antioxidant nutrient action, and these factors must be taken into consideration.

Although our study did not demonstrate a direct relation between inflammation and fat-soluble vitamins, it can be indirectly presupposed that the increase of proinflammatory substances originated from abdominal adiposity could distinctly affect different concentrations of vitamins according to gender. This study showed that boys had an increase in retinol and α-tocopherol, while β-carotene and 25(OH) were reduced in abdominal obesity. In girls, on the other hand, only α-tocopherol was increased in central adiposity. This difference may be due to variations existing between genders in the action of hormones on the effects of the inflammation mediated by obesity. With the increase of proinflammatory cytokines in obesity, there is the activation of the hypothalamic-pituitary-adrenal axis (HPA). In response to elevated cortisol levels, there is an increased deposition of visceral adipose tissue and a reduction of subcutaneous adipose tissue in men. However, in females, there is a gradual adaptation of the central fat deposition, since the deposition of adipocytes in the abdominal region increases, but the accumulation of fat in the upper and lower body parts decreases gradually, thus providing a protection to females from the inflammatory process of obesity [46].

Thus, boys are more likely to accumulate triglycerides in adipocytes of the central region, resulting in hypertrophy and increased production and secretion of adipokines to the bloodstream, whereas the gene expression of adipokines is positively correlated to the size of adipocytes [47]. Because of inflammation, initially there would be a greater mobilization of antioxidant vitamins in an attempt to fight oxidative stress, which could justify an increase of retinol and α-tocopherol. Beta-carotene, as well as having an antioxidant function and the possibility of being diverted for conversion to vitamin A in the liver, would likely decrease its concentrations during the inflammatory process. This increased demand for beta-carotene could explain the increased risk of beta-carotene inadequacy found in adolescents with abdominal obesity from both genders.

25(OH)D, however, may have its concentrations reduced because it is actively used by inflammatory cells, especially macrophages [48]. Moreover, 25(OH)D plasma concentrations are independently associated with PCR and albumin [49], i.e., in the presence of a systemic inflammation, the negative acute phase proteins, such as albumin, are reduced, which would decrease the transport of this vitamin in the bloodstream. Duncan et al. [39], evaluating PCR correlation coefficients compared with several micronutrients (including vitamin A, D and E) in the plasma of adult individuals, found a weak correlation, indicating that the association is highly variable from patient to patient, thus suggesting that the interpretation of plasma micronutrient deficiency should only be made when the presence of inflammation is ruled out.

Thus, the present study demonstrated that weight excess among teenagers might put these individuals at risk of metabolic inflammation when fat accumulation occurs in the abdominal region. In addition, the increase in abdominal fat followed different alterations in serum concentrations of soluble vitamins according to gender. Despite not having found a direct relation between inflammation and the evaluated vitamins, it is suggested that, during the biochemical interpretation of fat-soluble vitamins, factors such as obesity and inflammation be taken into account to avoid risking misinterpretation of such data. However, more studies are needed to better understand the mechanisms involved between the chronic inflammation process existing in obesity and the behavior of fat-soluble vitamins, their metabolic pathways and the mode of action in this process considering differences between genders.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1. Characteristics of adolescent students from Recife, northeastern Brazil, 2013.

Variables	n	%	CI 95%
Gender			
Boys	160	38,9	34,1-43,8
Girls	251	61,1	56,1-65,8
BMI/Age			
Weight excess	114	27,9	23,6-32,6
No weight excess	294	72,1	67,4-76,4
WC			
Normal	342	83,2	79,2-86,7
High	69	16,8	13,3-20,8
WHtR			
Normal	352	85,6	81,9-88,9
High	59	14,4	11,1-18,1
Serum Concentrations			
Retinol			
Adequate	265	67,9	63,1-72,6
Insufficient	125	32,1	27,4-36,9
β-carotene			
Adequate	84	25,9	21,2-31,0
Insufficient	240	74,1	68,9-78,7
α-tocopherol			
Adequate	47	11,9	8,9-15,5
Insufficient	347	88,1	84,4-91,1
25(OH)D			
Adequate	202	49,1	44,2-54,1
Insufficient	209	50,9	45,9-55,8
Food intake			
Vitamin A			
Adequate	199	49,8	44,7-54,7
Inadequate	201	50,3	45,2-55,2
Vitamin E			
Adequate	24	6,0	3,9-8,8
Inadequate	376	94,0	91,2-96,1
Vitamin D			
Adequate	1	0,2	0,0-1,3
Inadequate	410	99,8	98,8-99,9

BMI – body mass index; WC: waist circumference; CI – Confidence Interval; 25(OH)D: 25 Hydroxy-vitamin D; Adequate Retinol >0,7 µmol/L, Adequate β-caroteno: >0,9 µmol/L; Adequate α-tocoferol > 12 µmol/L; Adequate 25(OH)D: >72,4 nmol/L. Adequate food intake: vitamina A > 900mcg/day; vitamina E > 15 mg/day; vitamina D > 15mcg/day. Losts: BMI/Age by inconsistances between the two measurements, food intake of vitamin A and E for inconsistencies informations, serum retinol , β -carotene and α -tocopherol by biological material failure.

Table 2. Serum levels of α-1-acid glycoprotein according to nutritional status, serum concentrations and fat-soluble vitamin intake of adolescent students from Recife, northeastern Brazil, 2013.

	α -1-acid glycoprotein (g/L)						
		Boys			Girls		
	N	n	Mean ±SD	*p**	n	Mean ±SD	*p**
Nutricional status							
BMI/Age							
Weight excess	294	107	0,73±0,19	0,09	187	0,75±0,17	0,33
No weight excess	114	53	0,78±0,17		61	0,78±0,16	
WC							
Normal	342	121	0,73±0,19	0,04	221	0,75±0,17	<0,01
High	69	39	0,80±0,17		30	0,83±0,16	
WHtR							
Normal	352	130	0,73±0,19	0,03	222	0,75±0,17	0,06
High	59	30	0,81±0,17		29	0,81±0,16	
Serum concentrations							
Retinol							
Adequate	265	44	0,72±0,20	0,26	81	0,78±0,16	0,10
Insufficient	125	109	0,76±0,19		156	0,75±0,17	
α-tocopherol							
Adequate	47	27	0,82±0,16	0,03	20	0,77±0,13	0,88
Insufficient	347	126	0,73±0,19		221	0,76±0,17	
25(OH)D							
Adequate	202	96	0,73±0,18	0,27	106	0,75±0,16	0,58
Insufficient	209	64	0,77±0,19		145	0,76±0,18	
β-carotene							
Adequate	84	33	0,76±0,23	0,82	51	0,77±0,17	0,75
Insufficient	240	89	0,77±0,17		151	0,76±0,16	
Food intake							
Vitamin A							
Adequate	199	76	0,73±0,19	0,18	123	0,77±0,17	0,54
Inadequate	201	79	0,77±0,18		122	0,75±0,17	
Vitamin E							
Adequate	24	10	0,65±0,14	0,09	14	0,77±0,18	0,80
Inadequate	376	145	0,76±0,19		231	0,76±0,17	
Vitamin D							
Adequate	1	1	0,51	0,19	-	-	-
Inadequate	410	159	0,75±		251	0,75±0,17	

*Student's t Test unpaired

BMI: body mass index; WC: waist circumference; WHtR: *waist*-to-height ratio; SD: Standard deviation; 25(OH)D: 25 Hydroxy-vitamin D; Adequate Retinol >0,7 µmol/L, Adequate β-caroteno: >0,9 µmol/L; Adequate α-tocoferol > 12 µmol/L; Adequate 25(OH)D: >72,4 nmol/L.

Table 3. Serum concentrations of retinol, α-tocopherol, β-carotene and 25-hydroxy vitamin D according to body mass index (BMI), waist circumference (WC) and waist/height relation (WHtR) of adolescent students from Recife, Northeastern Brazil, 2013.

	n	Retinol (μmol/L) Mean ± SD	*p**	*n*	α-tocopherol (μmol/L) Median (QI)	*p***	*n*	β-carotene (μmol/L) Median (QI)	*p***	*n*	25(OH) D (nmol/L) Median (QI)	*p***
Boys												
BMI/Age												
Weight excess	53	0,97±0,35	0,02	51	7,94 (6,33-12,35)	0,02	44	0,8969 (0,8967-0,8975)	<0,001	53	68,25 (58,44-85,41)	0,001
No weight excess	102	0,84±0,32		102	6,75 (5,63-8,75)		78	0,8977 (0,8968-0,9249)		107	82,21 (67,42-101,14)	
WC												
High	39	1,02 ±0,37	0,03	37	8,56 (6,93-13,83)	0,003	35	0,8969 (0,8967-0,8976)	0,006	69	67,83 (58,34-80,89)	0,002
Normal	116	0,84 ±0,31		116	6,59 (5,51-8,64)		87	0,8975 (0,8967-0,9206)		121	81,12 (65,52-101,14)	
WHtR												
High	30	1,05 ±0,31	0,02	30	10,67 (7,24-17,12)	<0,001	28	0,8971 (0,8967-0,8978)	0,14	30	66,76 (58,99-75,69)	<0,001
Normal	125	0,85 ±0,33		123	6,64 (5,45-8,37)		94	0,8973 (0,8967-0,9159)		130	81,00 (64,97-102,05)	
Girls												
BMI/Age												
Weight excess	60	0,85±0,40	0,23	60	7,26(6,34-8,45)	0,03	52	0,8971(0,8968-0,8985)	0,08	61	66,30(57,12-78,67)	0,35
No weight excess	180	0,79±0,32		179	6,51(4,65-8,21)		148	0,89780(0,8970-0,9024)		187	68,72(59,02-82,21)	
WC												
High	29	0,87±0,46	0,26	29	7,42(6,60-8,89)	0,02	24	0,8971(0,8969-0,8979)	0,09	30	65,41(55,82-78,57)	0,26
Normal	213	0,80±0,32		212	6,62(4,74-8,19)		178	0,8977(0,8969-0,9022)		221	68,51(59,12-83,33)	
WHtR												
High	28	0,82±0,39	0,86	28	7,41(6,85-8,34)	0,03	24	0,8971(0,8969-0,8979)	0,10	29	66,53(56,08-78,67)	0,58
Normal	214	0,81±0,33		213	6,61(4,70-8,23)		178	0,8977(0,8969-0,9022)		222	68,38(58,49-82,54)	

*Student's t Test unpaired; ** Mann-Whitney Test;

BMI: body mass index; WC: waist circumference; WHtR: *waist*-to-height ratio; SD: Standard deviation; QI: Quartile Interval

Table 4. Factors associated with serum inadequacy of retinol, α-tocopherol, β-carotene and 25-hydroxy vitamin D in adolescent students from Recife, northeastern Brazil, 2013.

	Retinol (μmol/L)					α-tocopherol (μmol/L)					β-carotene (μmol/L)					25 (OH) D (nmol/L)				
		Insufficient					Insufficient					Insufficient					Insufficient			
	N	n	%	PR(CI95%)	p*	N	n	%	PR(CI95%)	p*	N	n	%	PR(CI95%)	p*	N	n	%	PR(CI95%)	p*
Boys																				
BMI/Age																				
Weight excess	52	11	21,2	1,00		51	37	72,5	1,00		44	40	90,9	1, 46 (1,2-1,8)	0,002	53	29	54,7	1, 67 (1,2-2,41)	0,01
No weight excess	101	33	32,7	1,54 (0,8-2,8)	0,19	102	89	87,3	1,20 (1,0-1,4)	0,04	78	49	62,8	1,00		107	35	32,7	1,00	
WC																				
High	38	6	15,8	1,00		37	25	67,6	1,00		35	32	91,4	1,40 (1,2-1,7)	0,007	39	22	56,4	1,63 (1,1-2,3)	0,03
Normal	115	38	33,0	6,33 (2,8-14,4)	<0,001	116	101	87,1	1,29 (1,02-1,6)	0,01	87	57	65,5	1,00		121	42	34,7	1,00	
WHtR																				
High	29	3	10,3	1,00		30	18	60,0	1,00		28	24	85,7	1, 24 (1,0-1,5)	0,014	30	19	63,3	1,83 (1,3-2,6)	<0,01
Normal	124	83	66,9	6,47 (2,2-19,9)	<0,001	123	108	87,8	1,46 (1,1-1,9)	<0,001	94	65	69,1	1,00		130	45	34,6	1,00	
Girls																				
BMI/Age																				
Weight excess	57	20	35,1	1,64 (0,7-1,6)	0,97	60	52	86,7	1,00		52	44	84,6	1,19 (1,0-1,4)	0,08	61	38	62,3	1,09 (0,9-1,4)	0,58
No weight excess	178	60	33,7	1,00		179	167	93,3	1,08 (0,97-1,2)	0,18	148	105	70,9	1,00		187	107	57,2	1,00	
WC																				
High	27	9	33,3	1,00		29	24	82,8	1,00		24	24	95,8	1,33 (1,2-1,5)	0,02	30	19	63,3	1,11 (0,8-1,5)	0,64
Normal	210	72	34,3	1,03 (0,6-1,8)	0,91	212	197	92,9	1,12 (0,95-1,3)	0,07#	178	128	71,9	1,00		221	126	57,0	1,00	
WHtR																				
High	25	8	32,0	1,00		28	25	89,3	1,00		24	23	95,8	1,33 (1,2-1,5)	0,02	29	29	65,5	1,15 (0,9-1,5)	0,48
Normal	212	73	34,4	1,08 (0,6-1,9)	0,98	213	196	92,0	1,03 (0,9-1,2)	0,71#	178	128	71,9	1,00		222	126	56,8	1,00	

*Chi-square Test; # Fisher's Exact Test/ BMI: body mass index; WC: waist circumference; WHtR: *waist*-to-height ratio; PR: Prevalence ration QI: Quartile Interval; 25(OH)D: Hidroxi-vitamin D; Adequate Retinol >0,7 μmol/L, Adequate β-caroteno: >0,9 μmol/L; Adequate α-tocoferol > 12 μmol/L; Adequate 25(OH)D: >72,4 nmol/L

8. CONSIDERAÇÕES FINAIS

Com base nos resultados dessa tese, pode-se concluir que:

- Os adolescentes apresentam risco de inadequação das vitaminas lipossolúveis, com importante déficit tanto no consumo alimentar, como nos níveis séricos.
- O comportamento metabólico das vitaminas A, D, E e β-caroteno parece diferir de acordo com o sexo e excesso de peso entre os adolescentes.
- O aumento da adiposidade abdominal cursa com alterações distintas nas concentrações séricas das vitaminas lipossolúveis de acordo com o sexo.
- O excesso de peso pode colocar os adolescentes em risco de inflamação metabólica quando o acúmulo de gordura ocorrer em região abdominal.

Sugerem-se como perspectivas:

- Investigar as rotas bioquímicas que cada vitamina lipossolúvel participa, especialmente no que diz respeito ao aumento da adiposidade.
- Aprofundar os estudos para melhor compreensão dos mecanismos envolvidos entre o processo inflamatório, obesidade e o comportamento das vitaminas lipossolúveis.
- Considerar a obesidade e inflamação, quando for interpretar as concentrações bioquímicas das vitaminas lipossolúveis nos adolescentes.
- Subsidiar futuras investigações sobre intervenções nutriiconais no tratamento da deficiência de vitaminas lipossolúveis em adolescentes.

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ANEXO 01: Parecer do Comitê de ética em pesquisa

UNIVERSIDADE FEDERAL DA PARAIBA - UFPB
HOSPITAL UNIVERSITÁRIO LAURO WANDERLEY - HULW
COMITÊ DE ÉTICA EM PESQUISA COM SERES HUMANOS - CEP

CERTIDÃO

Com base na Resolução nº 196/96 do CNS/MS que regulamenta a ética da pesquisa em seres humanos, o Comitê de Ética em Pesquisa do Hospital Universitário Lauro Wanderley - CEP/HULW, da Universidade Federal da Paraíba, em sua sessão realizada no dia 30/11/2010, após análise do parecer do relator, resolveu considerar **APROVADO** o projeto de pesquisa intitulado **DISLIPIDEMIA E SUA ASSOCIAÇÃO COM O EXCESSO DE PESO EM UMA COORTE DE ESCOLARES DO RECIFE-PE.** Protocolo CEP/HULW nº. 723/10, Folha de Rosto nº 286034, CAAE Nº 6527.0.000.126-10, da pesquisadora ***ILMA KRUZE GRANDE DE ARRUDA***.

Ao final da pesquisa, solicitamos enviar ao CEP/HULW, uma cópia desta certidão e da pesquisa, em CD, para emissão da certidão para publicação científica.

João Pessoa, 30 de novembro de 2010.

Iaponira Cortez Costa de Oliveira
Coordenadora do Comitê de Ética em Pesquisa - CEP/HULW

Profª Drª Iaponira Cortez Costa de Oliveira
Coordenadora do Comitê de Ética em Pesquisa-HULW

Endereço: Hospital Universitário Lauro Wanderley-HULW - 4º andar. Campus I - Cidade Universitária.
Bairro: Castelo Branco - João Pessoa - PB. CEP: 58051-900 CNPJ: 24098477/007-05
Fone: (83) 32167302 — Fone/fax: (083)32167522 E-mail - cephulw@hotmail.com

ANEXO 02: Comprovante de submissão do artigo 1

MS ID#: AJCN/2016/131979

MS TITLE: Prevalence and factors associated with fat-soluble vitamin deficiency in adolescents

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Sincerely,

Charlotte Phillips

Senior Peer Review Support Specialist

The American Journal of Clinical Nutrition

9650 Rockville Pike

Bethesda, MD. 20814-3990

Phone:301-634-7240

Fax:240-404-6798

Email: ajcnsubmit@nutrition.org

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ANEXO 03: Comprovante de submissão do artigo 2

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Manuscript #	2016EJCN0105
Current Revision #	0
Submission Date	31st Jan 16
Current Stage	Decision Sent to Author
Title	Adiposity, Inflammation And Fat-Soluble Vitamins in Adolescents
Running Title	Adiposity, Inflammation and Fat-Soluble Vitamins
Manuscript Type	Original Article
Special Issue	N/A
Category	Vitamins and plant food
Word Count	2830
Corresponding Author	Dr. Ilma Arruda (UFPE)
Contributing Authors	Dr. Rebecca Paes-Silva , Ms. Patricia Gadelha , Dr. Regiane Maio , Dr. Célia De Castro , Dr. Alcides Diniz
Abstract	Objective: Evaluate the association between inflammatory process, adiposity and vitamins A, D and E in adolescents. Methods: Transversal study with adolescents from 12 to 19 years old from both genders. A questionnaire to collect social and economic data, lifestyle and food intake of adolescents was used. Then, an anthropometric evaluation and a blood sampling were performed to analyze serum concentrations of α-1-acid glycoprotein (AGA), retinol, β-carotene, α-tocopherol and 25-hidroxi vitamin D (25(OH)D). Results: The levels of AGA were higher for abdominal obesity in both genders. Male adolescents with insufficient α-tocopherol serum levels had low levels of AGA (p=0.03) and an increased risk of 25(OH)D and β-carotene deficiency regarding total and abdominal fat; girls had an increased risk of insufficient β-carotene with abdominal obesity. Conclusion: Abdominal adiposity reflects a higher risk of inflammation and causes different changes to the concentration of fat-soluble vitamins according to gender.
Section Editor	Not Assigned
Techniques	Not Applicable;
Subject Terms	Health sciences/Health care Health sciences/Health care/Nutrition
Conflict of Interest Statement	There is **NO** conflict of interest to disclose.

Clinical Trial	No
Applicable Funding Source	National Research Council (CNPq) (process no. 473387/2010-2) and Ministry of Science and Technology (agreement IMIP/MCT, process no. 01. 0265.00/2005). [Arruda] National Research Council (CNPq) (process no. 473387/2010-2) and Ministry of Science and Technology (agreement IMIP/MCT, process no. 01. 0265.00/2005). [Paes-Silva] National Research Council (CNPq) (process no. 473387/2010-2) and Ministry of Science and Technology (agreement IMIP/MCT, process no. 01. 0265.00/2005). [Gadelha] National Research Council (CNPq) (process no. 473387/2010-2) and Ministry of Science and Technology (agreement IMIP/MCT, process no. 01. 0265.00/2005). [Maio] National Research Council (CNPq) (process no. 473387/2010-2) and Ministry of Science and Technology (agreement IMIP/MCT, process no. 01. 0265.00/2005). [De Castro] National Research Council (CNPq) (process no. 473387/2010-2) and Ministry of Science and Technology (agreement IMIP/MCT, process no. 01. 0265.00/2005). [Diniz]
Databank Requirements	I have no data to deposit in a repository

Manuscript Items

1. Author Cover Letter PDF (1339KB)
2. Merged File containing manuscript text and 4 Table files. PDF (485KB)
    a. Article File PDF (214KB)
    b. Table 1 PDF (88KB)
    c. Table 2 PDF (128KB)
    d. Table 3 PDF (35KB)
    e. Table 4 PDF (36KB)