Universidade do Estado do Rio de Janeiro
Centro Biomédico
Instituto de Nutrição

Paula Normando dos Reis Costa

Comprimento telomérico e sua associação com marcadores socioeconômicos e polimorfismos genéticos relacionados ao metabolismo de vitamina D: Estudo Pró-Saúde

Rio de Janeiro
2018

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Tese apresentada, como requisito parcial para obtenção de título de Doutor, ao Programa de Pós-Graduação em Alimentação, Nutrição e Saúde da Universidade do Estado do Rio de Janeiro. Linha de Pesquisa: Adaptações fisiológicas e metabólicas: Programação, nutrição e atividade física.

Orientadora: Prof.ª Dr.ª Flávia Fioruci Bezerra

Orientadora: Prof.ª Dr.ª Cíntia Santos-Rebouças

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DEDICATÓRIA

À professora Flávia Fioruci Bezerra, minha grande inspiração, que construiu esse sonho comigo ao longo de nove anos.

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RESUMO

NORMANDO, P. *Comprimento telomérico e sua associação com marcadores socioeconômicos e polimorfismos genéticos determinantes do estado de vitamina D:* Estudo Pró-Saúde. 2018. 152 f. Tese (Doutorado em Alimentação, Nutrição e Saúde) - Instituto de Nutrição, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2018.

O comprimento dos telômeros na vida adulta é reconhecido como um preditor consistente do início precoce de doenças cardiovasculares e metabólicas. O conhecimento dos determinantes sociais e biológicos do comprimento telomérico é fundamental para avaliar o risco de envelhecimento biológico precoce. Nesta Tese são apresentados dois manuscritos originais que investigaram a associação entre o CTL e marcadores socioeconômicos e demográficos (artigo 1), e a associação entre o CTL e concentrações séricas de 25(OH)D e polimorfismos de nucleotídeo único (SNPs) relacionados ao metabolismo da vitamina D (artigo 2). Trata-se de um estudo transversal conduzido com parte de uma coorte de funcionários de uma Universidade no Estado do Rio de Janeiro – o Estudo Pró-Saúde (n=470; 51 ± 8 anos; 52% mulheres). Informações sobre raça/cor da pele, escolaridade, estado civil, renda familiar, tabagismo, prática de atividade física e diagnóstico de doença crônica foram autorrelatadas durante a entrevista. O CTL de cada amostra foi mensurado por reação em cadeia da polimerase quantitativa em Tempo Real (qPCR). As concentrações séricas de 25(OH)D foram avaliadas por imunoensaio por quimiluminescência. As genotipagens dos polimorfismos (rs12785878, rs10741657, rs6013897 e rs2282679) foram realizadas por PCR em Tempo Real. No primeiro artigo, após o ajuste pela idade e potenciais co-variáveis relacionadas à saúde, uma menor escolaridade foi associada a um menor CTL somente nos homens (β = -0,05; 95% IC: -0,09, -0,01). Homens e mulheres apresentaram a correlação esperada entre a idade mais avançada e CTL mais curto (r = -0,19, $P < 0,01$ e r = -0,18, $P < 0,01$, respectivamente). No entanto, nos homens com menor escolaridade houve um gradiente mais acentuado na relação inversa entre o CTL e a idade (r = -0,31, $P < 0,01$). No segundo artigo, a subdivisão em quatro categorias segundo as concentrações séricas de 25(OH)D não apresentaram associação com o CTL ($P = 0,19$). Após ajustes por co-variáveis, os participantes com o genótipo CC (gene *GC* - rs2282679) apresentaram CTL significativamente menor do que aqueles com genótipos AC e AA (média ± EP: 0,50 ± 0,03, 0,58 ± 0,01 e 0,57 ± 0,01, respectivamente, $P < 0,05$). Utilizando modelos ajustados de regressão multivariada, o genótipo CC (gene *GC* - rs2282679) se associou inversamente ao CTL (β = -0,07; 95% IC: -0,13, -0,01). Nos homens, aqueles com os genótipos AC e CC (gene *GC* - rs2282679) apresentaram maior chance de ter CTL abaixo da mediana (0,54), quando comparados àqueles com genótipo AA (OR = 4,78; 95% IC: 1,19, 19,17 e OR = 4,61; 95% IC: 1,18, 17,90, respectivamente). Nossos resultados sugerem que a escolaridade pode ser um importante fator socioeconômico capaz de afetar o CTL, especialmente entre os homens. Além disso, também sugerimos que o SNP rs2282679, envolvido na síntese da proteína ligante de vitamina D (DBP), pode modular o comprimento dos telômeros, e SNPs associados ao metabolismo da vitamina D podem indicar de maneira mais fidedigna a influência desta vitamina sobre o comprimento dos telômeros.

Palavras-chave: Telômeros. Envelhecimento. Determinantes sociais em saúde. Vitamina D. SNP. Brasil.

ABSTRACT

NORMANDO, P. *Telomere length and its association with socioeconomic markers and genetic polymorphisms determinants of vitamin D status:* Pró-Saúde Study. 2018. 152 f. (Doutorado em Alimentação, Nutrição e Saúde) - Instituto de Nutrição, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2018.

Telomere length in adult life is a consistent predictor of earlier onset of cardiovascular and metabolic diseases. The knowledge of social and biological determinants of telomere length is critical to evaluate the risk of early biological aging. In this thesis we present two original manuscripts that investigated the association of LTL with socioeconomic and demographic markers (manuscript 1) and serum concentrations of 25(OH)D and single nucleotide polymorphisms (SNPs) related to vitamin D metabolism (manuscript 2). This is a cross-sectional study conducted with part of a cohort of employees from a University in the State of Rio de Janeiro - the Pró-Saúde Study (n = 470; 51 ± 8 years; 52% women). Information on race/skin color, educational attainment, marital status, household income, smoking status, physical activity and medical diagnoses of chronic disease were self-reported during the interview. The LTL of each sample was measured by quantitative Real-Time polymerase chain reaction (qPCR). Serum concentrations of 25(OH)D were evaluated by chemiluminescence immunoassay. The polymorphisms genotyping (rs12785878, rs10741657, rs6013897 and rs2282679) was performed by Real-Time PCR. In the first manuscript, after adjustment for age and potential health-related covariates, lower educational attainment was associated with shorter LTL only in men (β = -0.05; 95% CI -0.09, -0.01). Both women and men showed the expected relationship between older age with shorter LTL (r = -0.19, $P <$ 0.01 and r = -0.18, $P <$0.01, respectively). However, there was a more pronounced gradient in the inverse relationship between LTL and age in men with lower educational attainment (r = -0.31, $P <$0.01). In the second manuscript, categories of 25(OH)D serum concentrations were not associated with LTL (P = 0.19). After adjustments, participants with CC genotype (*GC* gene - rs2282679) had significantly shorter LTL than those with AC and AA genotypes (mean ± SE: 0.50 ± 0.03, 0.58 ± 0.01 and 0.57 ± 0.01, respectively, $P <$ 0.05). Using adjusted multivariate regression models, CC genotype (*GC* gene - rs2282679) was inversely associated with LTL (β = -0.07; 95% CI -0.13, -0.01). In men, those with AC and CC (*GC* gene - rs2282679) had higher odds ratio for LTL below the median (0.54), compared to those with AA genotype (OR= 4.78; 95% CI 1.19, 19.17, and OR=4.61; 95% CI 1.18, 17.90, respectively). Our results suggest that educational attainment may be an important socioeconomic marker that can affect LTL, especially among men. In addition, we also suggest that the SNP rs2282679, involved in the synthesis of vitamin D binding protein (DBP), can modulate LTL and SNPs associated with vitamin D metabolism may indicate more accurately the influence of this vitamin on telomere length.

Keywords: Telomere. Aging. Social determinants of health. Vitamin D. SNP. Brazil.

LISTA DE FIGURAS

LISTA DE TABELAS

ARTIGO 1

ARTIGO 2

LISTA DE ABREVIATURAS E SIGLAS

$1,25(OH)_2D$	1,25-di-hidroxivitamina D
1α-OHase	1α-hidroxilase
24-OHase	24-hidroxilase
25-OHase	25-hidroxilase
25(OH)D	25-hidroxivitamina D
BMI	Body mass index
CEP	Consubstanciado do Comitê de Ética em Pesquisa
CDK	Quinase dependente de ciclinas
CDKI	Inibidor de quinase dependente de ciclinas
CTL	Comprimento dos telômeros de leucócitos
CV	Coeficiente de Variação
DBP	Proteína ligante de vitamina D
EROs	Espécies reativas de oxigênio
FGF 23	Fator de crescimento de fibroblastos 23
FIOCRUZ	Fundação Oswaldo Cruz
GWAS	Genome-wide association studies
IBGE	Instituto Brasileiro de Geografia e Estatística
IGF-1	Fator de crescimento semelhante à insulina 1
IL-2	Interleucina 2
IL-6	Interleucina 6
IL-8	Interleucina 8
IL-12	Interleucina 12
IMC	Índice de massa corporal
kb	Quilobase (do inglês, *kilobase*)
LEING	Laboratório para Estudos da Interação entre Nutrição e Genética
LTL	Leukocyte telomere length
LSD	Least significant difference (*post hoc* teste)
NF-κB	Fator nuclear kappa B
OECD	Organisation for Economic Co-operation and Development
pb	Pares de Base
PBMC	Células mononucleares do sangue periférico (do inglês *Peripheral Blood Mononuclear Cell*)

PCR	Proteína C reativa
PNA	Ácido nucleico marcado
POT 1	Proteína protetora dos telômeros
PTH	Paratormônio
qPCR	Reacão em cadeia da polimerase quantitativa
RAP1	Repressor/ativador de proteína 1
ROS	Reactive oxygen species
RXRA	Receptor de ácido retinóico alfa
SD	Standard deviation
SE	Standard error
SNP	Polimorfismos de nucleotídeo único
TGF- β	Fator de crescimento transformante β
TIN2	Proteína de interação nuclear-TRF1 2
TNF-α	Fator de necrose tumoral
TPP1	Proteína de interação-TIN2 1
TRF	Fragmento de restrição terminal (em inglês *terminal restriction fragment*)
TRF1	Fator de repetição telomérica de ligação 1
TRF2	Fator de repetição telomérica de ligação 2
UCSF	Universidade da Califórnia San Francisco
UERJ	Universidade do Estado do Rio de Janeiro
UVB	Radiação ultravioleta B
VDR	Receptor de vitamina D
VDRE	Elementos de resposta à vitamina D (do inglês *vitamin D response element*)

SUMÁRIO

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