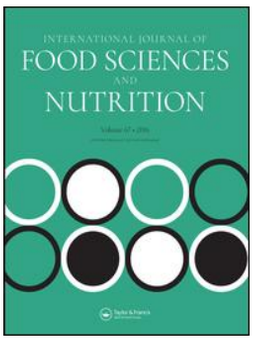

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RESEARCH ARTICLE

Milk intake and IGF-1 rs6214 polymorphism as protective factors to obesity

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ABSTRACT

Mexico ranks 2nd in adult obesity and 4th in milk intake worldwide. Low levels of IGF-1 have been related to obesity and can be reverted by milk intake. The rs6214 polymorphism has been associated with an increase in the expression of IGF-1. Therefore, the aim of the study was to evaluate the association between both, rs6214 polymorphism and milk intake, and obesity. We analysed 99 adult volunteers, with and without a history of milk intake, for the presence of this polymorphism through qPCR and body composition by electro-bioimpedance. Univariate logistic regression analyses showed that TT genotype is inversely associated with obesity and body fat mass. Besides, milk intake is also related to low obesity, body fat mass and visceral fat, and high percentage of lean mass. Multivariate logistic regression analyses confirm the univariate relationships, showing a clear inverted association between TT genotype, milk intake and obesity.

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IGF-1; obesity; BMI; rs6214

Introduction

Obesity is a chronic disease caused by the excessive accumulation of body fat, and it has been labelled as one of the major epidemics of the 21st century. According to a national survey on health and nutrition conducted in Mexico (ENSANUT 2016), 34.1% of adolescents from 12 to 19 years of age suffer from obesity, as well as 67.5% of adults over 20; these percentages represent a 10.5% increase with respect to 20121. Prevalence figures are similar in countries such as the United States, England, Canada, and Spain, among others (OECD 2017). In 2017 the Global Burden of Disease Collaborators reported that, in 2015, a total of 107.7 million children and 603.7 million adults were obese and that, since 1980, the prevalence of obesity has doubled in more than 70 countries and has continuously increased in most other countries. Besides, high BMI accounted for 4.0 million deaths worldwide, 40% higher than in non-obese people. More than two thirds of deaths related to high BMI were due to cardiovascular disease (The GBD 2015 Obesity Collaborators 2017).

In most cases, the origin of obesity is multifactorial; it includes biological, genetic, metabolic, endocrinologic, environmental, and behavioural elements (Kadouh and Acosta 2017). The excess of fatty tissue can result in clinical problems due to endocrinological and metabolic disruptions such as hyperinsulinemia, hyperleptinemia, decreased levels of adiponectin and ghrelin, and increased levels of free cortisol (Simona et al. 2015); evidence of alterations in the regulation, secretion, and metabolism of different hormones has been reported (Baudrand et al. 2010; García-Solís et al. 2018). Some of these alterations can be reversed by decreasing body weight, for instance hyperinsulinism and the hyposecretion of the growth hormone (GH) (Álvarez-Castro 2011). Obesity is characterised by a decreased secretion of GH, which is proportional to body mass index (BMI) (Álvarez-Castro 2011). GH is responsible for the expression of insulin like growth factor type I (IGF-I)(Aguirre et al. 2016), also called somatostatin, which exerts mitogenic and anabolic actions in different tissues (García-Solís et al. 2018). IGF1 is regulated by age and nutritional status (Giustina et al. 2008; Claessen et al. 2016). In this

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respect, there is evidence that milk intake is related to increase in IGF-1 circulating levels in human beings (Hoppe et al. 2005).

Some of the primary roles of IGF-1 are promoting protein synthesis and inhibiting protein degradation, as well as inducing myoblast fusion through the positive regulation of the synthesis of interleukin-13 and the skeletal muscle (Yang et al. 2015; Herbert et al. 2017). Muscle mass is not affected by increased levels of IGF-1; however, when IGF-1 levels are low, muscle mass is reduced (Yang et al. 2015).

There are approximately 7000 single nucleotide polymorphisms (SNPs) in the IGF-1 gene; among the most important are rs10860864, rs2373721, rs7136446, rs10778176, rs12821878 rs35767, rs3110697, and rs6214 (D'Aloisio et al. 2009). The rs6214 SNP of the IGF-1 gene has been associated with high serum levels of IGF-113.

On the basis of these data, the purpose of the present study was to evaluate the effect of milk intake and the presence of IGF-1 rs6214 polymorphism on obesity.

Materials and methods

Study design

This research is a Case and control study design according milk consumption, performed between August 2015 to December 2018. The study was carried out in accordance with the Helsinki Declaration and Good Clinical Practices (GCP), and the protocol was approved by the research ethics committee of the "Dr. Santiago Ramón y Cajal" General Hospital, ISSSTE (CONBIOETICA 10CE100120130723 and COFEPRIS 13 CEI 10005 128). All participants signed an informed consent agreement.

Study population

A total of 99 apparently healthy men and women from the state of Durango (México), aged between 20 and 59 years, volunteered for the study. Target population consisted of 62 cases of whole milk consumer participants, and control population included 37 no milk consumer participants (in any formulation); groups were classified according to BMI. Participants suffering from severe hepatic disorders, pregnant women, and people who consumed steroids or thyroid hormones were excluded from the study. The smoking status (positive or negative), socioeconomic qualification (high, medium and low), marital status (single or married) and physical activity (high, medium and low) were also recorded.

Dietary assessment

Milk intake and exclusion criteria were determined using a questionnaire administered to all participants. The questionnaire included total intake of dairy whole liquid milk. Minimum milk products intake per day to be considered milk consumer was established at 200 mL of whole milk, according to Guías Alimentarias y de Actividad Física para Población Mexicana (2015).

Evaluation of body composition

Weight and body composition parameters were obtained using body composition monitoring equipment (Omron HBF-516 and Tanita TBF-300A). BMI, body fat, fat mass, metabolic age, metabolic rate, percentage of fat, and weight data from the 99 volunteer participants were obtained. Obesity was considered with a BMI $> 25\,kg/m^2$. The height and weight measurements were performed in centimetres and kilograms, respectively, with the volunteer without shoes and with the head at a 90° angle between the chin and chest.

Molecular assays

The following (molecular biology grade) reagents were acquired from Sigma-Aldrich (St. Louis, Missouri, United States): dodecyl trimethyl ammonium bromide (DTAB), hexadecyltrimethylammonium bromide (CTAB), chloroform, methanol, Milli-Q water, and NaCl.

Blood samples were obtained by venipuncture after participants had fasted for 8–10 h. Samples were kept in Vacutainer™ tubes containing EDTA as an anticoagulant.

Genomic DNA was obtained from whole blood using the DTAB-CTAB method (Gustincich et al. 1991); DNA integrity and purity were assessed and samples were stored at −20°C until further genotyping analyses. The polymorphism of rs6214 C > T IGF-1 gene was analysed by real-time PCR using a StepOne™ system (Applied Biosystems, Thermo Fisher Scientific corporation, Foster City, California, United States) and the specific *TaqMan*™ probe C_11495137_10 for IGF-1 rs6214 gene polymorphism (Context Sequence: TCACATCTAACTATGACAGAA AACA[**C/T**] GTTAAGTCTGCAGAAGACTGCCTAT).

Statistical analyses

Participant's sociodemographic factors and milk intake are presented as percentages. Anthropometric

measurements were reported as medians for each value. The Hardy–Weinberg equilibrium test was used to characterise groups. It was performed by comparison of observed and expected genotype frequencies using χ^2 goodness-of-fit test. ($\chi^2_{\alpha\,=\,0.05}$, 1 d.f.= 3.84). Odds ratios (OR) and 95% confidence intervals (CI) were reported, calculated using 2x2 tables by testing three genetic models of inheritance, i.e. dominant, codominant and recessive models. We performed univariate and multivariate logistic regression analyses. A p-value of ≤ 0.05 was considered statistically significant for all calculations. All statistical calculations were performed with StatSoft STATISTICA™ 10.0 (Dell Software Inc., Oklahoma United States).

Results

The distribution of variables, sex, age, and BMI with respect to milk intake are shown in Table 1. No significant differences with respect to milk products intake were found in terms of age and sex. Statistically significant differences were found between BMI and milk intake among people into the ranges of 18.5–24.9 and 25–29.99 of BMI ($p = 0.039$ and 0.045, respectively). Moreover, when we group people in <25 BMI and >25 a more significant association was observed ($p = 0.0001$). Similarly, body composition parameters appear to be related with milk intake; significant associations ($p < 0.05$) were observed between milk intake and body fat mass ($p = 0.0006$), visceral fat ($p = 0.022$) and lean mass ($p = 0.0017$).

Table 1. Characteristics of the population based on milk consumption.

	Milk intake ($n = 62$)	No milk intake ($n = 37$)	X^2 p value**
Age (years), N (%)			
20–29	29 (29.29)	7 (7.07)	0.254
30–39	12 (12.12)	7 (7.07)	0.345
40–49	11 (11.11)	12 (12.12)	0.567
50–59	10 (10.10)	11 (11.11)	0.132
Sex, N (%)			
Men	32 (32.32)	12 (12.12)	0.063
Women	30 (30.30)	25 (25.25)	0.075
BMI*, N (%)			
18.5–24.99	28 (28.28)	6 (6.6)	0.039
25–29.99	20 (20.20)	16 (16.16)	0.045
30–34.99	8 (8.08)	10 (10.10)	0.674
35–39.99	5 (5.05)	3 (3.03)	0.765
>40	1 (1.01)	2 (2.02)	0.675
≥25	34 (34.34)	31 (31.31)	0.0001
Body Composition %, Average (SD)			
Body Fat Mass	27.58 (13.21)	36.95 (9.40)	0.0006
Lean Mass	52.70 (10.62)	50.36 (9.62)	0.0017
Visceral Fat	7.56 (3.61)	9.68 (4.20)	0.022

*BMI = Body Mass Index (kg/m^2); SD = standard deviation.
**$p < 0.05$ is considered as statistically significant.

Both groups the milk intake and non milk intake populations were found to be in agreement with Hardy-Weinberg equilibrium for the IGF-1 polymorphism ($x^2_{0.05,1d.f.} = 3.84$).

Table 2 shows a univariate logistic analysis of the association between IGF-1 rs6214 C > T polymorphism, according to inheritance models and body composition parameters. Statistically significant inverted associations ($p < 0.05$) were observed between the presence of the mutated allele in heterozygote and/or homozygote genotypes and fat content. In fact, single T allele by itself is significantly and inversely related with obesity (OR = 0.40, 95% CI [0.21–0.75], $p = 0.004$) and directly with lean mass (OR = 2.16, 95% CI [1.18–3.94], $p = 0.011$).

Milk intake was also found to be inversely associated with body fat mass (OR = 0.20, 95% CI [0.08–0.50], $p = 0.0006$), visceral fat (OR = 0.29, 95% CI [0.10–0.84], $p = 0.022$).) and obesity (OR = 0.32, 95% CI [0.11–0.80], $p = 0.0001$), and directly associated with lean mass (OR = 5.09, 95% CI [1.83–14.10], $p = 0.002$).

Finally, Table 3 shows a multivariate analysis including IGF-1 rs6214 genotypes in different inheritance models, and milk intake in relation to obesity. The results show a significant inverted association between TT genotype (OR = 0.25, 95% CI [0.04–0.87], $p = 0.048$), the combination of TT + CT genotypes in relation to CC genotype (dominant model) (OR = 0.38, 95% CI [0.16–0.90], $p = 0.025$) and milk intake (OR = 0.28, 95% CI [0.10–0.74], $p = 0.011$).

Discussion

The lack of significant differences in milk intake as a function of age in the studied population is because milk intake in Mexico remains similar throughout people's lives, unlike customs in other countries (Servicio de Información Agroalimentaria y Pesqueria 2017). Most people within the normal BMI range were aged between 20 and 30 years; as reported by ENSANUT (2016), BMI tends to increase with age.

Our results show that the highest percentage of participants (28.28%) with normal weight range (18–24.9 BMI) is in the group of people whose milk intake was at least 1 glass per day (milk intake group). Conversely, in the no milk intake group there was a very low percentage of normal weight people (6.6%), giving rise the idea that milk intake is a protective factor for obesity, which was confirmed through both, the univariate logistic analysis (Table 2) (OR = 0.32,

Table 2. Univariate logistic analysis of the association between obesity and body composition of subjects, in relation to milk intake and the presence of the IGF-1 C > T (rs6214) polymorphism.

	Body fat mass			Lean mass			Visceral fat			$^{+}$Obesity		
	OR*	IC_{95}**	*p* value	OR*	IC_{95}**	*p* value	OR*	IC_{95}**	*p* value	OR*	IC_{95}**	*p* value***
Milk intake												
No		Ref.			Ref.			Ref.			Ref.	
Yes	0.20	0.08-0.50	0.0006	5.09	1.83-14.10	0.002	0.29	0.10-0.84	0.022	0.32	0.11-0.80	0.0001
Codominant model												
CC		Ref.			Ref.			Ref.			Ref.	
CT	0.94	0.39-2.25	0.900	2.88	1.19-6.92	0.025	0.71	0.26-1.88	0.48	0.50	0.19-1.30	0.154
TT	0.22	0.05-0.90	0.033	3.3	0.91-11.87	0.120	0.40	0.1-1.51	0.17	0.19	0.05-0.66	0.009
Dominant model												
CC		Ref.			Ref.			Ref.			Ref.	
TT + CT	0.71	0.32-1.60	0.410	2.68	1.19-6.0	0.016	0.61	0.25-1.50	0.28	0.38	0.16-0.90	0.029
Recessive model												
CC + CT		Ref.			Ref.			Ref.			Ref.	
TT	0.23	0.06-0.86	0.028	1.80	0.53-6.09	0.330	0.47	0.13-1.62	0.23	0.26	0.08-0.84	0.023
C Allele		Ref.			Ref.			Ref.			Ref.	
T Allele	0.57	0.31-1.05	0.073	2.16	1.18-3.94	0.011	0.62	0.32-1.20	0.15	0.40	0.21-0.75	0.004

*OR: Odds Ratio; **IC: Confidence interval 95%, ***$p < 0.05$ is considered as statistically significant; $^{+}$obesity = BM1 > 25 kg/m^2.

Table 3. Multivariate logistic regression analysis of obesity^{+}.

Variable	OR*	IC_{95}**	*p* value***
Genotype IGF-1 (rs6214)			
CC	Ref.	–	–
CT	2.08	0.49-8.72	0.314
TT	0.25	0.04-0.87	0.048
CT + TT	0.38	0.16-0.90	0.025
CC + CT	Ref.	–	–
TT	0.46	0.11-1.96	0.30
Milk intake			
No	Ref	–	–
Yes	0.28	0.10-0.74	0.011

*OR = Odds Ratio; **IC = Confidence interval 95%.
***$p < 0.05$ is considered as statistically significant; $^{+}$obesity = BM1 > 25 kg/m^2.
p value model = 0.016; pseudo R2 = 0.09157.

CI95% [0.11–0.8], $p = 0.0001$) and the multivariate logistic analysis (Table 3) (OR = 0.28, CI95% [0.10–074], $p = 0.011$). This is in concordance with previous results presented by Bell-Serrat and his collaborators (Bel-Serrat et al. 2014) who demonstrated that consumption of dairy milk products correlates with BMI values within the normal range. Our results are also consistent with several other studies, including results from Rodriguez-Rodriguez et al. (2010) where it was demonstrated a relationship among consumption of dairy milk products and BMI values within the normal weight range (OR = 0.23, CI95% [0.08–0.66]). Besides, less body fat and less trunk fat has also been reported (Zemel et al. 2005) as well as a negative correlation with metabolic risk (-0.044 ± 0.01, $p = 0.009$) (OR = 0.531, CI95% [0.302–0.931])(Bermúdez et al. 2015; Drehmer et al. 2016).

The association between milk intake and a BMI within the normal range could be due to certain components of milk, such as milk proteins (Gilbert et al. 2011; Abreu et al. 2014; Astrup et al. 2015), calcium (Villarroel et al. 2014; Booth et al. 2015) and conjugated linoleic acid (CLA)(Bendtsen et al. 2013; Yang et al. 2015); a low intake of calcium in the diet has been associated with stimulation of lipogenesis and reduced lipolysis resulting from changes in intracellular calcium flux, whereas diets including higher calcium contents promote thermogenesis and reduced adiposity in human and animal models (Zemel and Zhao 2009; Fernández Fernández et al. 2015). Moreover, CLA consumption has been associated with increased HDL cholesterol and decreased LDL cholesterol (Park and Pariza 2007; Chen et al. 2012; Kim et al. 2016; Ferlay et al. 2017), as well as increased energy expenditure and expression of uncoupling proteins, modulation of adipokines and cytokinesis, and less fat mass resulting from the lower presence of fat cells (Park and Pariza 2007; Kim et al. 2016).

The present study suggests that the presence of rs6214 polymorphism of IGF-1 gene is associated with healthy BMI values (<24.99) and high levels of lean. Such polymorphism is located in a non-translated 3' region, which could be increasing the role and the structure of RNAs, including the regulation and translation of messenger RNAs into proteins (Sadee et al. 2011; Buroker 2016). This mechanism induces an increased expression of IGF-1, which in turn promotes the synthesis of proteins in the skeletal muscle and its regulation during growth (Grounds 2002; Yang et al. 2015). In this respect, an study by Velloso (2008) reported an association between high levels of IGF-1, responsible for the presence of polymorphism, and increased muscle mass, which could explain the results obtained in the present study. The interaction between milk consumption and the presence of IGF-1 polymorphism in relation to obesity, can be due to CLA, a peroxisome proliferator (Belury et al. 1997; Belury 2002; Sandoval et al. 2009; Ramiah et al. 2015,

2016) that has an important role in the alteration of genetic expression (Lemberger et al. 1996; Zhao et al. 2015; Ramiah et al. 2016) stimulating the biological actions of IGF-1: cell survival and division (Lennon et al. 2002; Zhao et al. 2015). Conversely, results obtained by Yang et al.40, who associated the presence of rs6214 polymorphism with low appendicular musculoskeletal mass differ from our results, probably as a result of the differences between study populations; Yang et al. worked with a Chinese elderly adult population (aged 70–75), whereas our study used an age range from 20 to 59 years of age. The loss of muscle mass among elderly adults is a natural phenomenon, therefore, polymorphism cannot be directly associated with low appendicular musculoskeletal mass.

Conclusions

Results obtained in the present study allow us to suggest that people carrying T allele of the IGF-1 rs6214 polymorphism and concomitantly consume milk regularly and is favoured to maintain within the normal weight range (18–24.99). Consequently, milk intake and the presence of the variant allele of IGF-1 rs6214 polymorphism might be relevant factors in the prevalence of obesity among inhabitants of Durango, México.

Disclosure statement

The authors report no conflict of interest.

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