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ORIGINAL CONTRIBUTION

Associations between lactase persistence and the metabolic syndrome in a cross-sectional study in the Canary Islands

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Abstract
Background The single nucleotide polymorphism (SNP) LCT −13910 C>T, associated with genetically determined phenotypes of lactase persistence (LP) or non-persistence (LNP), was studied in relation to the metabolic syndrome (MS).
Aim of the study The aim was to determine if milk intake and MS are associated. We applied Mendelian randomization (MR). The SNP, LCT −13910 C>T, with the genotypes LP (TT/CT) and LNP (CC), was taken as a proxy for milk consumption.
Methods A representative sample of adults belonging to the Canary Islands Nutrition Survey (ENCA) in Spain aged 18–75 years ($n = 551$) was genotyped for the LCT −13910 C>T polymorphism. We used the International Diabetes Federation (IDF) criteria to define MS.
Results 60% of the population was LP and 40% LNP. One hundred seven LP subjects (35.0%) and 53 LNP subjects (25.6%) showed MS ($\chi^2 = 5.04$, $p = 0.025$). LP subjects showed a significantly higher odds ratio (OR) for MS than LNP subjects computed for the whole population: both the crude OR (1.56; 95% CI 1.06–2.31) and adjusted OR for sex, age, daily energy intake, physical activity and educational level (1.57; 95% CI 1.02–2.43). Adjusted OR for women with LP was 1.93; 95% CI 1.06–3.52.
Conclusions The T allele of the SNP might constitute a nutrigenetic factor increasing the susceptibility of LP subjects, especially women, to develop MS in the Canary Islands.

Keywords LCT −13910 C>T polymorphism · Metabolic syndrome · Milk · Mendelian randomization · Nutrigenetics

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Introduction

Lactase non-persistence is defined as the inability to digest the disaccharide lactose (milk sugar), an inherited condition characterized by the reduced production of lactase after weaning [41]. A SNP located 14 kb upstream of the lactase gene (LCT −13910 C>T) has been shown to be associated with lactase persistence in Europids. The T allele appears to be dominant over the C allele that represents LNP [14]. Lactase persistence (CT/TT genotype) is thus a dominant trait controlled by the lactase gene (LCT). Lactase non-persistence (CC genotype) is also known as adult-type hypolactasia (AtH) or primary hypolactasia [36]. Homozygosity for the C allele contributes to the restricted consumption of fresh milk and dairy products to approximately 12 g lactose or two cups of milk daily in adults and

some children and adolescents [40]. Recent studies, nevertheless, provide evidence of at least three other SNPs in close vicinity to the LCT −13910 C>T polymorphism associated with LP in some African populations [24, 42].

Metabolic syndrome is a concept that assembles risk factors for cardiovascular disease (CVD) and type 2 diabetes into a defined clinical phenotype. Heritability studies demonstrate that there are marked genetic influences affecting several features of MS [25]. Also, gender-specific factors contributing to the development of MS have been identified [35]. We used the International Diabetes Federation (IDF) to determine MS [2]. The criteria of MS can be interlinked and their co-occurrence has been found to be associated with increased cardiovascular disease (CVD) risk and morbidity [10, 17]. CVD is the first cause of death in European countries and is estimated to affect one of every four Spaniards [4].

Increases in milk consumption, especially the low fat variety, are widely promoted as healthy beverages with protective effects against metabolic syndrome [13, 33] and high blood pressure [5, 16]. Some studies suggest that dairy products may help prevent weight gain and promote weight loss [44]. Other studies conclude that dairy or calcium consumption alone does not result in weight or fat loss in the short or long term [26, 34]. Researchers have also suggested that milk avoidance is associated with a reduced risk of insulin resistance and metabolic syndrome [27].

The role milk consumption plays, as a nutrigenetically influenced modifiable factor, in the development of MS is controversial. Therefore, we conducted a study based on the concept of Mendelian randomization (MR) to investigate possible associations between genetically determined phenotypes of LP and LNP subjects and metabolic syndrome. The aim was to determine if the LCT −13910 C>T polymorphism is associated with MS using MR. This question was examined in an available Canary Islands population where, in contrast to rest of Spain, there is a high prevalence of co-occurring cardiovascular risk factors and one of the highest cardiovascular mortality rates of the country.

Methods

Population

A representative sample of the Canarian general population, aged 6–75 years, was selected using a two-stage stratified sampling method from a total of 1,747 individuals who participated in the Canary Islands Nutrition Survey (ENCA 1997–1998). Anthropometrics and blood pressure were measured. A representative subsample of 782 subjects was randomized to participate in the biochemical assessment. The present study is based on 551 adults aged 18–75 years (240 men and 311 women) with complete genetic data. Sociodemographic and lifestyle variables including age, sex, educational level, smoking, alcohol consumption and physical activity were recorded. Details on data collection have been published elsewhere [21, 37, 38]. The definition of MS used in this study is the one established by the International Diabetes Federation (IDF) [2].

Genetic analysis

Genomic DNA was isolated from the EDTA whole blood samples of individuals using the QIAamp DNA Blood Mini Kit spin procedure. The DNA fragment spanning the −13910-C/T polymorphic site was amplified using a biotinylated forward primer (5′-GGGCTGGCAATACAGATAAGATA-3′) and an unbiotinylated reverse primer (5′-AGCAGGGCTCAAAGAACAATCTA-3′). PCR amplifications were carried out in a 5 µl volume containing the forward and reverse primers, 2.5 units of Taq polymerase, 2.0 mmol/l $MgCl_2$ and 0.2 mmol/l each of dGTP, dATP, dTTP, and dCTP. As templates, 100 ng of the extracted genomic DNA was added. The PCR products were prepared for Pyrosequencing according to a standard protocol (Pyrosequencing AB, Uppsala, Sweden) using 20 µl amplicon captured by streptavidin-coated Sepharose beads and the Pyrosequencing Sample Preparation Kit (Pyrosequencing AB, Uppsala, Sweden). The applied sequencing primer was 5′-CTTTGAGGCCAGGG-3′. Sequencing was performed using a PSQ96 SNP reagent Kit and a PSQ 96MA system (Pyrosequencing AB) PSQ 96MA 2.0.1 software. The procedure has been previously described in detail [30].

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as means and standard deviations. Differences between LP and LNP subjects with regard to continuous variables were calculated by Student *t* tests. Differences in the prevalence of MS between LP and LNP were calculated by means of χ^2 analyses. A multivariate logistic regression was used to calculate the odds ratios (ORs) of MS among LP and LNP subjects. The ORs were adjusted for sex (prior to stratification for sex), age, physical activity (sedentary, light, moderate and vigorous), educational level (less than elementary, elementary, high school, university) and daily energy intake (kcal/day). Statistical significance was set at 0.05, and confidence intervals at 95%. All analyses were conducted using SPSS for Windows (version 15.0; SPSS Chicago, IL, USA).

Ethics

The Institutional Committee of Ethics of the Canarian Health Service approved the study. All study patients submitted informed, written consent forms.

Results

In the current study, 551 subjects [240 men (43.6%) and 311 women (56.4%)], aged 18–75 years, were genotyped for the LCT −13910 C>T polymorphism. Seventy-two (13.1%) subjects were homozygous for LP (TT), 258 (46.8%) were heterozygotes (CT) and 221 (40.1%) were homozygous for LNP (CC). Thus, 59.9% showed the genetically determined LP phenotype (CT/TT genotypes) and 40.1% the phenotype LNP (CC genotype).

LP subjects consumed statistically significantly more milk than LNP subjects (300 g/day in average among LP subjects and 250 g/day in average among in LNP subjects, $p = 0.001$, Student's t test; Table 1). Daily energy intake did not differ significantly between LP and LNP subjects. LP subjects consumed in average 1,670 kcal/day and LNP subjects consumed in average 1,690 kcal/day (Table 1). LP women consumed about 300 g milk daily and had an energy intake of about 1,490 kcal/day. LNP women consumed about 252 g milk and 1,480 kcal daily. LP men consumed daily about 300 g milk and 1,910 kcal/day. LNP men consumed about 240 g milk and had a daily energy intake of 1,940 kcal/day.

Table 1 Descriptive characteristics of LP and LNP subjects

Characteristic	LP ($n = 330$)	LNP ($n = 221$)
Age, years	45.9 (14.8)	44.8 (15.0)
Sex (%)		
Women	192 (61.7)	119 (38.3)
Men	138 (57.5)	102 (42.5)
Energy intake, kcal/day	1,666 (349)	1,691 (349)
Milk intake, g/day*	300 (199.9)	246 (168.3)
Physical activity (%)		
Sedentary	213 (60.9)	137 (39.1)
Light	79 (57.2)	59 (42.8)
Moderate	27 (58.7)	19 (41.3)
Vigorous	5 (55.6)	4 (44.4)
Education (%)		
Less then elementary	113 (59.8)	76 (40.2)
Elementary	96 (64.9)	52 (35.1)
High school	74 (53.2)	65 (46.8)
University	46 (63.9)	26 (36.1)

*$p = 0.001$ (Student t test)

The frequency of MS did not vary significantly between both sexes (also using ATP-III criteria, data not shown). Plasma glucose levels did not differ between both sexes. We observed, however, a statistically significant difference in plasma triglyceride levels between men and women: men showed plasma triglyceride levels (mg/dl) of 133; 95% CI 122.7–143.0 and women showed plasma triglyceride levels (mg/dl) of 117; 95% CI 110.0–124.4, $p = 0.011$ (Student's t test).

Differences between the LCT C>T −13910 genotypes in singular components of MS are presented in Table 2. The most prevalent component of MS according to the IDF criteria was central obesity. One hundred ninety-five (62%) LP subjects and 109 (56%) LNP subjects showed a waist circumference (WC) beyond the cut-off stipulated by IDF. Also, the numbers and percentage of LP and LNP subjects meeting the IDF definition for MS are shown in Table 2. LP subjects showed a statistically significantly higher frequency of MS when compared to LNP subjects (107 (35%) LP subjects and 53 (26%) LNP subjects met the definition for MS, $p = 0.025$, χ^2 test; Table 2).

Table 3 shows the OR of MS for LP and LNP subjects stratified by sex, and using multivariate logistic regression analysis. Table 3 also displays the crude OR and the OR of MS adjusted for sex, daily energy intake (kcal/day), physical activity and educational level according to IDF criteria. In Table 3, LP subjects showed a significantly higher OR for MS than LNP subjects computed for the whole population, in both the crude and adjusted model (OR_{crude}, 1.56; 95% CI 1.06–2.31, and $OR_{adjusted}$, 1.57; 1.02–2.43). LP women showed a significantly higher OR of MS compared to LNP women in the adjusted model (1.93;

Table 2 Number of subjects with LP and LNP who fulfill the different criteria for MS

IDF criteria	LP ($n = 313$)	LNP ($n = 211$)
Blood pressure		
SBP ≥130 and/or DBP ≥85	89 (28.4)	53 (25.1)
HDL cholesterol		
HDL <40 mg/dl (M), <50 mg/dl (W)	118 (37.7)	62 (29.4)
Triglyceridemia		
Triglycerides >150 mg/dl	88 (28.1)	49 (23.2)
Central obesity		
Waist circ. ≥94 (M), ≥80 (W)	195 (62.3)	109 (55.9)
Glycaemia		
Fasting glucose ≥100 mg/dl	64 (20.4)	35 (16.6)
Metabolic syndrome*	107 (35.0)	53 (25.6)

Percentages in brackets

*$\chi^2 = 5.04$, $p = 0.025$; missing because of incomplete data, 38 subjects

Table 3 Odds ratio (OR) for the presence of MS in subjects with LP and LNP

	OR (95% CI)	*p*	OR (95% CI)	**p*
All ($n = 513$)				
LNP ($n = 207$)	Ref		Ref	
LP ($n = 306$)	1.56 (1.06–2.31)	0.025	1.57 (1.02–2.43)	0.041
Women ($n = 291$)				
LNP ($n = 111$)	Ref		Ref	
LP ($n = 180$)	1.64 (0.97–2.77)	0.067	1.93 (1.06–3.52)	0.031
Men ($n = 222$)				
LNP ($n = 96$)	Ref		Ref	
LP ($n = 126$)	1.47 (0.82–2.64)	0.196	1.22 (0.64–2.34)	0.549

*Adjusted for sex (prior to stratification), age, energy intake, physical activity and educational status

Missing because of incomplete data, 38 subjects

95% CI 1.06–3.52). Men did not show a significant association of LP with MS, in the crude and adjusted model (OR_{crude}, 1.47; 95% CI 0.82–2.64, and $OR_{adjusted}$ 1.22; 95% CI 0.64–2.34). Substituting the ATP-III criteria for the IDF criteria when defining MS did not substantially change these results (data not shown).

Discussion

The main result of this study is that subjects with LP (LCT −13910 genotype CT and TT) had a higher OR for MS than subjects with LNP (LCT −13910 genotype CC). The OR was also statistically significant for women after adjusting for nutritional and environmental factors. In men, a similar but weaker trend was found, which did not reach significance.

Given the global increase in the prevalence of MS, there is a need to understand how metabolic risk factors are influenced by potentially modifiable lifestyle behaviors such as physical activity and nutrition. A complex interplay between gene or gene cluster and environment might be necessary for the expression of the MS phenotype. Accordingly, the association of population genomics with epidemiological studies can help to identify why certain populations are more susceptible to develop MS, CVD and type 2 diabetes than others [28]. The frequency of LP varies significantly in different populations, being most prevalent in North Western Europe. In Sweden, the frequency of LP is about 90% compared to 60% we found in the Canary Islands [3].

In the Canary Islands, LP subjects consumed in average about 17% more milk compared to LNP subjects. In Spain, generally, consumption of 'milk' is high and similar to the quantities of milk consumed in Nordic countries, noted also in this study, irrespective of the LCT C>T −13910 genotype. Furthermore, highest milk consumption in Spain is found in the Canary Islands [6, 39]. These observations constitute an exception to the north–south pattern in milk and milk product consumption across Europe [22]. Thus, results of genetic epidemiological studies obtained in one defined population should not be applied without reserve to other populations or ethnics.

Not only interethnic differences can influence the development of MS, but also gender-specific differences can come into play [9, 12, 15, 35]. The latter has led to the recommendation to focus on the identification of gender-specific criteria for risk management in patients with MS [29, 35].

Bovine milk consumption gives rise to insulinemic responses far beyond what could be expected from its glycemic index (GI) [32] and drinking large amounts of milk may provide excess energy [8]. Potential factors, thus, contributing to the 57% higher risk of LP subjects compared to LNP subjects to develop MS in the Canary Islands. Interestingly, lactase persistent women showed a 93% higher risk to develop MS compared to a 22% higher risk in LP men, after adjustment for the main nutritional and environmental variables. We did not find, nevertheless, a significant difference in milk consumption between women and men in their respective LP or LNP group. This means that the quantity of milk consumed by women and men in their corresponding LP or LNP group cannot explain higher risk of LP women to develop MS compared to LP men.

Milk contains hormonal constituents that influence endogenous hormones in sufficient quantities to have biological effects in consumer. Milk consumption increases insulin-like growth factor-I plasma levels [1, 7, 20, 23, 43]. Furthermore, because of contemporarily production methods, modern cow milk has a high content of sex steroids and precursors of sex steroids such as progesterone [18, 19]. Progesterone and other steroid hormones have been associated with markers of insulin resistance [9]. These factors could shed light on the observed higher risk of LP women to develop MS compared to LP men in the Canary Islands. In addition, sex steroids, especially testosterone, can influence the physiologically already different adiponectin plasma levels in women and men [31].

Nevertheless, there are other factors that also could influence development of MS in LP or LNP. Fermentation of lactose in the colon could, e.g., lead to increase plasma levels of short chain fatty acids, which in turn could increase insulin sensitivity in LNP subjects [11].

There are several limitations that need to be considered when interpreting the findings of this study. The cross-sectional design limits inferences of causality and its direction. Also, the relatively low number of subjects involved in this study limits inferences of causality. In addition, the observed differences in the OR of MS by LP/LNP between sexes should be interpreted with caution. Although we have controlled for the main confounders

(sex, age, daily energy intake, physical activity and educational level), it is possible that other unmeasured confounders, e.g., early life programing and ethnic affiliation, could explain our findings. In addition, our results should be interpreted with caution outside Southern Europe. Therefore, gender-related susceptibility requires further investigation in other populations.

This study points to a significant association of LP with MS in the Canary Islands. LP is accompanied by a higher consumption of milk compared to LNP. In the Canary Islands, consumption of milk is high and comparable or even higher than in some Nordic countries. LP subjects of the Canary Islands exhibited a 57% higher risk to develop MS compared to LNP subjects. LP women showed a higher risk to develop MS compared to LP men. Increased milk consumption of LP women compared to LP men was not found, and therefore, cannot explain the higher risk of LP women to develop MS compared to LP men.

In conclusion, in the Canary Islands, the T allele of the SNP, LCT C>T −13910, might constitute a nutrigenetic factor increasing the susceptibility of subjects with LP, especially women, to develop MS.

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