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Original article

Influence of nutrition on somatotropic axis: Milk consumption in adult individuals with moderate-severe obesity

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SUMMARY

Background & aims: Nutrition is the major environmental factor that influences the risk of developing pathologies, such as obesity. Although a number of recent reviews pinpoint a protective effects of milk on body weight and obesity related co-morbidities, an inaccurate estimate of milk might contribute to hamper its beneficial effects on health outcomes. Seven-day food records provide prospective food intake data, reducing recall bias and providing extra details about specific food items. Milk intake stimulates the somatotropic axis at multiple levels by increasing both growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secretion. On the other hand, obesity is associated with reduced spontaneous and stimulated GH secretion and basal IGF-1 levels. Aim of this study was to evaluate the milk consumption by using the 7-days food record in obese individuals and to investigate the association between milk intake and GH secretory status in these subjects.

Methods: Cross-sectional observational study carried out on 281 adult individuals (200 women and 81 men, aged 18–74 years) with moderate-severe obesity (BMI 35.2–69.4 kg/m^2). Baseline milk intake data were collected using a 7 day food record. Anthropometric measurements and biochemical profile were determined. The GH/IGF-1 axis was evaluated by peak GH response after GHRH + ARGININE and IGF-1 standard deviation score (SDS).

Results: The majority of individuals (72.2%) reported consuming milk; 250 mL low-fat milk was the most frequently serving of milk consumed, while no subjects reported to consume whole milk. Milk consumers *vs* no milk consumers presented the better anthropometric measurements and metabolic profile. At the bivariate proportional odds ratio model, after adjusting for BMI, age and gender, milk consumption was associated the better GH status (OR = 0.60; $p < 0.001$). Among milk consumers, subjects consuming 250 mL reduced-fat milk *vs* 250 mL low-fat milk presented the better anthropometric measurements and metabolic profile. At the bivariate proportional odds ratio model, after adjusting for BMI, age and gender, the consume of 250 mL reduced-fat milk was associated better GH status (OR = 0.54; $p = 0.003$).

Conclusions: A novel positive association between milk consumption, GH status, and metabolic profile in obese individuals was evidenced. Regardless of the pathogenetic mechanisms, this novel association might be relevant in a context where commonly obese individuals skip breakfast, and suggests the need of a growing cooperation between Nutritionists and Endocrinologists in the management of the obese patients.

Abbreviations: BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor 1; IGF-1 (SDS), insulin-like growth factor 1 standard deviation score; SBP, systolic blood pressure; DBP, diastolic blood pressure; PTH, parathyroid hormone; HoMA-IR, homeostasis model assessment – insulin resistance; HDL, High-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, Alanine transaminase; γGT, γ-glutamyltransferase; MetS, metabolic syndrome.

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1. Introduction

Nutrition is the major environmental factor, directly under human control, that interacts with genetic predisposition and influences the risk of developing pathologies, such as obesity and diabetes. Milk, with cheese and yogurt, is one of the three most commonly consumed dairy products. Most countries have quantitative recommendations that usually range from 2 to 3 servings or cups of milk or yogurt or sometimes the equivalent serving of cheese [1]. In Italy it is recommended to consume *per* day 250 mL of milk [2]. A number of recent reviews pinpoint a protective effects of dairy products on health outcomes [1], body weight [3] and obesity related co-morbidities, including type 2 diabetes and cardiovascular disease [4,5]. However, the relative contribution of the nutritional components of milk in these associations still remains inconclusive. In addition, milk consumption is often targeted in obese individuals to reduce saturated fatty acids, the intake of which is commonly discouraged in current dietary guidelines [6]; moreover, eating behavior in obese individuals is often characterized *per se* by skipping breakfast [7], traditionally the main meal of the day where Italians mostly consume milk [8].

A possible source of uncertainty in the beneficial effects of milk in the vast majority of the studies might result from an inaccurate estimate of milk intake due to the use of retrospective methods of dietary assessment or from too demanding food frequency questionnaires. By contrast, 7-days food record provide prospective food intake data. In particular, 7-days food diary are recorded at the same time of consumption, reduce the recall bias and provide extra details about the types and amounts of specific food items. Recently, a prospective study using dietary data from 7-days food record reported the association between the consumption of specific dairy products and a decreased risk of type 2 diabetes [4].

Several studies have consistently shown that high milk intake exerts relevant effects on somatotropic axis, an integrated endocrine system also involved in body weight balance [9]. In particular, milk intake stimulates the somatotropic axis at multiple levels by increasing both growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secretion [10–12]. On the other hand, obesity is associated with reduced spontaneous and stimulated GH secretion and basal IGF-1 levels [13]. Both central and peripheral factors might account for this condition of functional low GH status in obesity, including nutritional-driven components, insulin-glucose homeostasis, and circulating free fatty acids (FFA) [14]. Currently, no studies on the regulation of the somatotropic axis by dietary factors, mainly milk intake, were carried out using a dynamic evaluation of GH secretion and the 7-days food record in obesity.

The aims of this study are twofold. Firstly, to evaluate the intake, frequency, and type of milk consumed, derived from the 7-days food record in obese individuals. Secondly to investigate the association between milk intake and GH secretory status in these subjects.

2. Materials and methods

2.1. Subjects and methods

2.1.1. Design and setting

This is a cross-sectional observational study carried out at the Department of Clinical Medicine and Surgery of the University of Naples Federico II (Italy) from July 2013 to February 2015. The procedures used were in accordance with the guidelines of the Helsinki Declaration on human experimentation. The study was approved by the Ethics Committee of the Federico II University Medical School of Naples (n.5/14). The purpose of the protocol was clearly explained to all the participants. The study was conducted without support from the pharmaceutical industry.

2.1.2. Population study

After obtaining written informed consent, 421 adult individuals (>18 years of age), who were referred to our unit for bariatric surgery evaluation, were consecutively enrolled. Criteria for exclusion from the study were current use of medications affecting calcium homeostasis and fat metabolism, including calcium and vitamin D (8 subjects), corticosteroids (10 subjects), antacids and proton pump inhibitors (15 subjects), bile-acid sequestrants and lipase inhibitors (7 subjects). Moreover, individuals with concurrent medical illness, such as neoplastic diseases (1 subject), renal diseases (2 subjects), malabsorptive disorders (5 subjects), inflammatory bowel diseases (9 subjects) and lactose intolerance (15 subjects), were excluded. Finally, we excluded from the study subjects following a specific dietary regimen for any reason (2 vegan subjects), those reporting to eat dairy foods more than once *per* week (55 subjects), and those drinking special milks, such as goat's and soy milk, and fermented milk as kefir and yoghurt (11 subjects).

Therefore, a total of 281 participants (200 women and 81 men, aged 18–74 years) with moderate-severe obesity (Body Mass Index (BMI): 35.2–69.4 kg/m^2), remained for analysis.

2.1.3. Dietary assessment

Dietary assessment and baseline milk intake data were collected using a 7 day food record [15,16]. Milk consumption was estimated using photographs representing portion sizes and household measures. The day one of the diary nutritionists trained to standardised protocols provided participants with instructions on how to complete the diary at the health check and asked participants to recall the previous day's intake. Participants prospectively completed the remaining 6 days. The subjects returned the records to the nutritionist who asked supplemental questions, if necessary. From these records the total amount of milk consumed was estimated, being the sum of the milk taken in milk containing drinks and with breakfast cereals. According to the Italy Food Guide Pyramid [2], the reference serving size of milk is 125 mL, equal to a glass of milk. It is recommended *per* day to consume 250 mL of milk (2 reference amounts).

The milk consumption was evaluated as: 1. Consumption (yes/no); 2. Type of milk consumed (whole milk, reduced-fat milk, and low-fat milk); 3. Serving of milk consumed (small serving, 125 mL; regular serving, 250 mL and large serving, 375 mL). 4. Daily average of total milk consumed during the seven days (<250 mL/day, =250 mL/day, >250 mL/day); 5. Consumption and type of milk (250 mL reduced-fat milk daily/other servings and types of milk).

Data were stored and processed using a commercial software (Terapia Alimentare Dietosystem® DS-Medica, http://www.dsmedica.info). The data were also compared with the tables of food consumption and recommended dietary intakes of the BDA (Food Composition Database for Epidemiological Studies in Italy) Italian National Institute of Nutrition and Food Composition Database in Italy (www.inran.it).

2.1.4. Anthropometric measurements

All anthropometric measurements were taken with subjects wearing only light clothes and without shoes. In each subject, weight and height were measured to calculate the BMI [weight (kg) divided by height squared (m^2), kg/m^2]. Height was measured to the nearest 1 cm using a wall-mounted stadiometer. Body weight was determined to the nearest 50 g using a calibrated balance beam scale. Waist Circumference (WC) was measured to the closest 0.1 cm with a non-extensible tape at the natural indentation or at a

midway level between the iliac crest and the lower edge of the rib cage if no natural indentation was visible. The measurement was made with the subject standing upright, feet together and arms hanging freely at the sides, with the subjects standing and breathing normally. In all individuals were measured Systolic (SBP) and diastolic (DBP) blood pressure in three times, 2 min apart, with a random zero sphygmomanometer (Gelman Hawksley Ltd., Sussex, UK) after the subject had been sitting for at least 10 min. The average of the second and third reading was recorded.

Information on smoking habit, alcohol consumption, and physical activity was obtained by a standard questionnaire. Current smokers were defined as those who smoked at least one cigarette *per* day and former smokers as those who had stopped smoking more than 1 year before the interview; the rest of the participants were defined as noncurrent smokers. Participants were also classified according to their alcohol intake into two groups: at least one glass of wine (or an equivalent amount of other alcoholic beverages *per* day) (YES) or no alcohol consumption (NO). Physical activity level was expressed according to whether the participant habitually engaged at least 30 min/day of aerobic exercise (YES/NO).

2.1.5. Definition of conventional risk factors

Obesity: The degree of obesity was established according to a scale based on BMI cut-off points: 35–39.9 kg/m^2 (grade II obesity or moderate obesity) and ≥40 kg/m^2 (grade III obesity or severe obesity), respectively. Abdominal obesity was defined as: WC ≥ 102 cm in men and ≥88 cm in women. *Hypertension was defined as*: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg on two different occasions or taking antihypertensive medication. *Hypercholesterolaemia was defined as*: a fasting blood total cholesterol level ≥190 mg/dL or use of lipid-lowering medication, and *hypertriglyceridaemia* as fasting blood triglyceride levels ≥150 mg/dL or use of lipid-lowering medication [17]. *Diabetes*: A history of using hypoglycemic agents or a type 2 diabetes was diagnosed according to ADA criteria [18].

2.1.6. Criteria to define metabolic syndrome

According to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III definition, metabolic syndrome (MetS) is present if three or more of the following five criteria are met: WC ≥ 102 cm (men) or 88 cm (women), blood pressure ≥130/85 mmHg, fasting triglyceride level ≥150 mg/dL, fasting high-density lipoprotein (HDL) cholesterol level ≤40 mg/dL (men) or ≤50 mg/dL (women), and fasting glucose ≥ 100 mg/dL [19].

2.1.7. Biochemical measurements

Samples were collected between 8 and 10 a.m. after an overnight fast of at least 8 h, with the individuals were in the resting position, and stored at −80 °C until being processed. All biochemical analyses including fasting plasma glucose, total cholesterol, fasting plasma triglycerides, total proteins and albumin, total calcium, creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT), γ-glutamyltransferase (γGT) were performed with a Roche Modular Analytics System in the Central Biochemistry Laboratory of our Institution. Low-density lipoprotein (LDL) and HDL cholesterol were determined by direct method (homogeneous enzymatic assay for the direct quantitative determination of LDL and HDL cholesterol). Corrected serum calcium was calculated (corrected calcium [mg/dL] = serum calcium [mg/dL] + 0.8 [4−serum albumin [g/dL]]). Intact parathyroid hormone (PTH) was measured by immunometric assay (Immulite iPTH; Diagnostic Products, Los Angeles, CA); the intra- and interassay CV were <7.0% and <5.5%, respectively. Fasting insulin levels were measured by a solid-phase chemiluminescent enzyme immunoassay using a commercially available kits (Immunolite Diagnostic Products Co, Los Angeles, CA). The intra-assay coefficients of variations (CV) for insulin was <5.5%. Homeostasis Model Assessment of Insulin Resistance (HoMA-IR) was calculated according to Matthews et al. [20]: a value of HoMA-IR >2.0 was set as stringent measure of insulin resistance.

The GH/IGF-1 axis was evaluated by measuring the GH peak after GHRH + ARGININE (ARG) and assay of circulating IGF-1 levels. The GH releasing hormone (RH) (1–29, Geref, Serono, Rome, Italy) + ARG (arginine hydrochloride, Salf, Bergamo, Italy) was performed according to Ghigo et al. [21] The GH response after ARG + GHRH was classified as deficient (GHD) when the GH peak was ≤4.2 μg/L and sufficient (GHS) when the GH peak was ≥4.2 μg/L [22]. Serum GH levels were measured by immunoradiometric assay (IRMA) using commercially available kits (HGH-CTK-IRMA, Sorin, Saluggia, Italy). The sensitivity of the assay was 0.02 μg/L. The intra- and interassay coefficients of variations (CVs.) were 4.5% and 7.9%, respectively. IGF-1 levels were classified as deficient when the standard deviation score (SDS) from the mean was <−2 for age and gender and sufficient when the SDS ranged from >−2 to 2.24 [23]. Serum IGF-1 levels were measured by IRMA after ethanol extraction (DSL Inc, Webster, TX); assay sensitivity was 0.8 μg/L; the normal ranges in adults aged 20–40 and 41–60 years were 110–494 and 100–300 μg/L, respectively. The intra-assay CVs. were 3.4%, 3.0% and 1.5% for the low, medium and high points of the standard curve, respectively. The interassay CVs. were 8.2%, 1.5% and 3.7% for the low, medium and high points of the standard curve, respectively.

2.1.8. Statistical analysis

Results are expressed as mean ± SD or as median plus range according to variable distributions evaluated by Kolmogorov–Smirnov test ($p < 0.001$). Differences between groups were analyzed by unpaired *t* test or Mann–Whitney *U*-test, as appropriate. When more than two groups were compared, analyses of variance (ANOVA) or Kruskal–Wallis test were performed, as appropriate, followed by Bonferroni post hoc analysis. The chi square (χ^2) test was used to determine the significance of differences in frequency distributions. Proportional odds ratio (OR) models were performed to assess the association among quantitative variables and qualitative variables (milk consumption: yes/no; type of milk: reduced-fat/low-fat milk; amount/type milk consumption: 250 mL reduced-fat milk/250 mL low-fat milk and servings of milk consumption: 125/250/375 mL). In these analyses, we entered only those variables that had a p value < 0.05 in the univariate analysis. To avoid multicollinearity, variables with a variance inflation factor (VIP) > 10 were excluded. Values ≤ 5% were considered statistically significant. Data were stored and analyzed using the MedCalc® package (Version 12.3.0 1993–2012 MedCalc Software bvba − MedCalc Software, Mariakerke, Belgium). Proportional odds model was carried out using the R Project for Statistical Computing 2014 (http://www.R-project.org).

3. Results

A higher percentage of obese participants were non-smokers (72%), non-alcohol users (82%), and sedentary (80%). Socio-demographic, anthropometric and metabolic characteristics of 281 obese individuals included in the study are summarized in Table 1. The majority of participants presented severe obesity and were females. In particular, 55 individuals (19.6%) were moderately obese and 226 individuals (80.4%) were severely obese. According to peak GH response and IGF-1 SDS, 169 individuals (60.1%) and 194 individuals (69.0%) presented GHD and IGF-1 deficiency, respectively. Impaired fasting glucose was diagnosed in 24.2% (68 pts), type 2 diabetes in 39.1% (110 pts), HoMA-IR >2 in 77.9% (219 pts),

Table 1
Socio-demographic, anthropometric measures and metabolic profile of 281 obese patients included in the study.

Parameters	
Age (years)	37.1 ± 12.1
Gender (Females)	200 (71.2%)
BMI (kg/m^2)	44.1 (35.2–69.4)
Peak GH response (μg/L)	2.5 (0.1–18.6)
IGF-1 (μg/L)	138.0 (35.0–483.0)
IGF-1 (SDS)	−2.7 (−6.1 to 5.9)
Waist circumference (cm)	130.8 ± 17.8
SBP (mmHg)	130.0 (80.0–180.0)
DBP (mmHg)	80.0 (50.0–110.0)
Total Calcium (mg/dL)	9.4 ± 0.5
Corrected Calcium (mg/dL)	9.0 ± 0.5
PTH (pg/mL)	48.0 (15.6–138.0)
Fasting Glucose (mg/dL)	94.0 (61.0–299.0)
Fasting Insulin (μU/mL)	18.0 (4.7–63.4)
HoMA-IR	4.2 (0.8–38.7)
Creatinine (mg/dL)	0.7 (0.5–1.4)
Serum albumin (g/dL)	4.5 ± 0.3
Total serum proteins (g/dL)	7.5 (6.0–8.8)
Total cholesterol (mg/dL)	186.4 ± 45.6
HDL cholesterol (mg/dL)	48.0 (10.0–98.0)
LDL cholesterol (mg/dL)	106.4 ± 46.8
Fasting Triglycerides (mg/mL)	149.0 (44.0–583.0)
AST (U/L)	29.0 (7.0–153.0)
ALT (U/L)	37.0 (5.0–202.0)
γGT (U/L)	36.0 (8.0–242.0)

The majority of participants presented severe obesity and were females. Results are expressed as mean ± SD or as median plus range according to variable distributions evaluated by Kolmogorov–Smirnov test. ***BMI***, body mass index; ***GH***, growth hormone; ***IGF-1***, insulin-like growth factor 1; ***IGF-1*** (***SDS***), insulin-like growth factor 1 standard deviation score; ***SBP***, systolic blood pressure; ***DBP***, diastolic blood pressure; ***PTH***, parathyroid hormone; ***HoMA-IR***, homeostasis model assessment - insulin resistance; ***HDL***, High-density lipoprotein; ***LDL***, low-density lipoprotein; ***AST***, aspartate aminotransferase; ***ALT***, Alanine transaminase; ***γGT***, γ-glutamyltransferase.

hypertension in 35.2% (99 pts) and MetS in 47.3% (133 pts). Socio-demographic, anthropometric measurements and metabolic characteristics of 281 obese participants according to GH status are reported in Table 2. As expected, obese individuals with both GHD and IGF-1 deficiency (146 pts), presented the worst anthropometric measurements and metabolic profile compared with obese counterparts with normal peak GH response (64 pts) or with those with GH/IGF-1 discordance (71 pts).

Figure 1 shows the milk intake in our group of obese participants. Among obese individuals, only less than 1/3 of participants reported not consuming milk and skipping breakfast. By contrast, the majority of individuals (203 pts) reported consuming milk; in particular, 250 mL low-fat milk was the most frequently serving of milk consumed, while no subjects reported to consume whole milk. In addition, breakfast was the only meal time where participants reported consuming milk servings, while there were no gender differences in types or amounts of milk consumption ($p = 0.461$ and $p = 0.974$, respectively). Total energy intake was not significantly different between milk consumers and no milk consumers (2289.0 ± 355.9 *vs* 2308.2 ± 454.8 kcal; $p = 0.712$).

The peak GH response was sufficient in 52.2% milk consumers *vs* 7.7% no milk consumers ($\chi^2 = 44.76$; $p < 0.001$). Table 3 summarizes the clinical characteristics of milk consumers according to milk servings. The best anthropometric measurements and metabolic profile were observed in subgroup of obese individuals consuming 250 mL servings of milk. In addition, this subgroup presented the highest peak GH response and IGF-1 SDS. In particular, the peak GH response was sufficient in 71.4% consumers of 250 mL milk *vs* 32.4% and 50.9% consumers of < or >250 mL milk, respectively ($\chi^2 = 22.61$; $p < 0.001$). Table 4 summarizes the clinical characteristics of the consumers of 250 mL of milk according to milk type. As seen in Table 4, the subgroup of the consumers of

Table 2
Anthropometric measures and metabolic profile of 281 obese patients according to GH status.

Parameters	GH − IGF-1 deficit	GH− IGF-1 sufficiency	GH/IGF-1 discordance	*p*-value
	n = 146 (52%)	n = 64 (23%)	n = 71 (25%)	
Age (years)	35.9 ± 11.3	40.0 ± 13.0	37.1 ± 12.1	0.073
BMI (kg/m^2)	47.6 (36.2–67.6)	40.0 (35.2–69.4)	43.7 (35.2–58.2)	**<0.001**
Waist circumference (cm)	135.9 ± 17.5	119.7 ± 16.6	130.4 ± 14.8	**<0.001**
SBP (mmHg)	130.0 (90.0–180.0)	120.0 (100.0–170.0)	130.0 (80.0–180.0)	**<0.001**
DBP (mmHg)	85.0 (60.0–110.0)	62.5 (60.0–110.0)	80.0 (50.0–100.0)	**<0.001**
Peak GH response (μg/L)	0.2 (0.0–4.1)	7.9 (4.2–18.6)	4.7 (0.1–17.0)	**<0.001**
IGF-1 (μg/L)	115.0 (35.0–183.0)	235.5 (132.4–231.0)	159.0 (56.4–483.0)	**<0.001**
IGF-1 (SDS)	−3.3 (−6.1 to −2.0)	−6.2 (−2.0 to 5.9)	−2.4 (−4.9 to 2.9)	**<0.001**
PTH (pg/mL)	59.4 (15.8–138.0)	39.4 (20.0–109.0)	42.8 (15.6–106.0)	**0.004**
Total Calcium (mg/dL)	9.4 ± 0.5	9.5 ± 0.5	9.5 ± 0.4	0.121
Corrected Calcium (mg/dL)	9.0 ± 0.5	9.1 ± 0.5	9.0 ± 0.4	0.519
Fasting Glucose (mg/dL)	106.0 (68.0–269.0)	85.0 (61.0–243.0)	94.0 (61.0–299.0)	**<0.001**
Fasting Insulin (μU/mL)	24.3 (5.0–61.5)	9.1 (4.7–63.4)	15.8 (15.0–46.3)	**<0.001**
HoMA-IR	6.5 (1.0–38.7)	1.9 (0.8–38.0)	3.6 (1.0–20.7)	**<0.001**
Creatinine (mg/dL)	0.7 (0.5–1.3)	0.7 (0.5–1.1)	0.8 (0.5–1.4)	0.063
Serum albumin (g/dL)	4.4 ± 0.3	4.4 ± 0.4	4.5 ± 0.3	0.403
Total serum protein (g/dL)	7.4 (6.0–8.6)	7.7 (6.1–8.8)	7.5 (6.0–8.7)	**0.007**
Total cholesterol (mg/dL)	194.2 ± 45.8	174.3 ± 47.6	181.3 ± 40.	**0.008**
HDL cholesterol (mg/dL)	45.5 (25.0–98.0)	53.5 (27.0–72.0)	49.0 (10.0–85.0)	**0.004**
LDL cholesterol (mg/dL)	114.7 ± 47.4	92.9 ± 48.7	101.6 ± 40.3	**0.005**
Fasting Triglycerides (mg/dL)	155.0 (44.0–480.0)	144.5 (53.0–256.0)	141.0 (50.0–583.0)	0.097
AST (U/L)	30.0 (8.0–116.0)	28.5 (7.0–101.0)	29.0 (7.0–153.0)	0.750
ALT (U/L)	33.0 (9.0–199.0)	42.5 (5.0–177.0)	37.0 (6.0–202.0)	0.172
γGT (U/L)	41.0 (11.0–232.0)	29.0 (8.0–108.0)	35.0 (13.0–242.0)	**0.004**
MetS (n, %)	92 (63.0%)	14 (21.9%)	27 (38.0%)	**<0.001**

The majority of obese subjects were GHD and IGF-1 insufficient. As expected, this subgroup presented the worst anthropometric measurements and metabolic profile. Metabolic syndrome was diagnosed according to the NCEP ATP III (ref# 19 in the text). Results are expressed as mean ± SD or as median plus range according to variable distributions evaluated by Kolmogorov–Smirnov test. Differences between groups were analyzed by ANOVA or Kruskal–Wallis test, when appropriate. The chi square (χ^2) test was used to determine significance differences in frequency distributions of MetS. A *p* value in bold type denotes a significant difference ($p < 0.05$). ***BMI***, body mass index; ***SBP***, systolic blood pressure; ***DBP***, diastolic blood pressure; ***GH***, growth hormone; ***IGF-1***, insulin-like growth factor 1; ***IGF-1*** (***SDS***), insulin-like growth factor 1 standard deviation score; ***PTH***, parathyroid hormone; ***HoMA-IR***, homeostasis model assessment - insulin resistance; ***HDL***, High-density lipoprotein; ***LDL***, low-density lipoprotein; ***AST***, aspartate aminotransferase; ***ALT***, Alanine transaminase; ***γGT***, γ-glutamyltransferase; ***MetS***, metabolic syndrome.

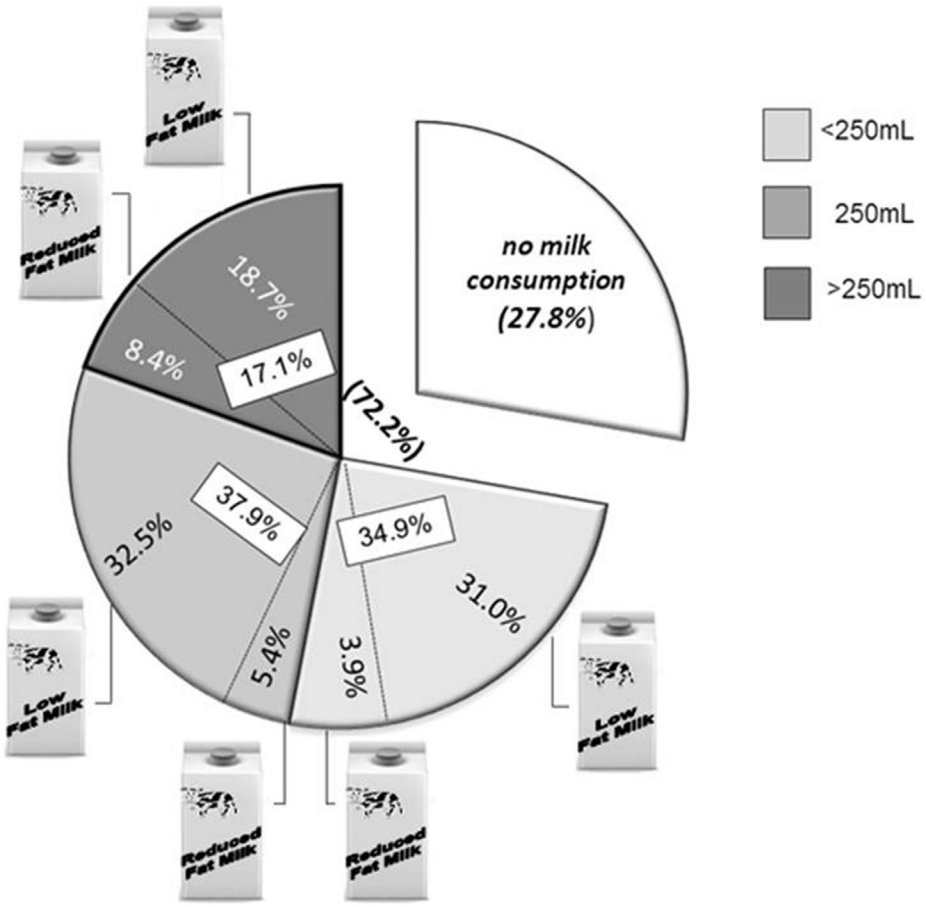

Fig. 1. Milk intake in 281 obese patients. Among obese patients milk was consumed by the majority of subjects (203 pts); in particular, 250 mL low-fat milk was the serving most frequently consumed. No subjects reported to consume whole milk. Results are expressed as percentage. Small serving, 125 mL; Regular serving, 250 mL; Large serving, 375 mL.

250 mL reduced-fat milk presented better metabolic profile, anthropometric measurements and GH status compared with those consuming low-fat milk. In particular, the peak GH response was sufficient in 78.8% consumers of 250 mL reduced-fat milk *vs* 27.3% consumers of 250 mL low-fat milk ($\chi^2 = 9.87$; $p = 0.002$).

Figure 2 shows the peak GH response and IGF-1 SDS levels in the study population grouped according to the amount of milk consumption and BMI. In both patients with moderate and severe obesity the prevalence of individuals with a normal peak GH response and normal IGF-1 SDS levels were higher among individuals consuming the 250 mL serving of milk compared with those consuming different servings.

3.1. Correlation studies

A bivariate proportional odds ratio model was performed to assess the association of milk consumption (yes/no) with anthropometric measures and metabolic profile. As expected, milk consumption was associated with anthropometric measurements, SBP/DBP, PTH, total calcium and corrected calcium, HoMA-IR, lipid profile, ALT, γGT and MetS (Table 5). Table 6 shows the multivariate proportional odds ratio model performed to assess the association among three different servings of milk with the GH status. According to the servings of milk, after adjusting for BMI, age and gender, the subjects consuming 250 mL presented the best GH status. Table 7 shows the bivariate proportional odds ratio models, performed to assess the association of milk consumption (yes/no; model 1) and type of milk (reduced-fat/low-fat milk; model 2), with the GH status. The subjects consuming milk, in particular reduced-fat milk have higher peak GH response and IGF-1 SDS than those not consuming milk or consuming low-fat milk, after adjusting for BMI, age and gender. Table 8 gives the bivariate proportional odds ratio model performed to assess the association of 250 mL reduced-fat milk or 250 mL low-fat milk. After adjusting for BMI, age and gender, subjects consuming 250 mL reduced-fat milk have higher peak GH response and IGF-1 SDS than those consuming 250 mL low-fat milk.

4. Discussion

In this observational study using the dietary intake data from 7-days food record, we found that in our series of obese Italian adults less than 1/3 of participants reported not consuming milk and skipping breakfast. In line with the Italian guidance [2], the 250 mL of milk was consumed by the majority of the participants. In particular, 250 mL reduced-fat milk was most frequently consumed serving of milk, breakfast was the only meal time where participants reported consuming milk, and there were no gender differences in milk consumption. As novel findings, using a dynamic evaluation of GH secretion, we found that among milk consumers peak GH response was sufficient in more than one-half of participants, despite obese individuals are frequently characterized by a functional low GH status. In particular, after adjusting for BMI, age and gender, the subgroup of obese individuals consuming 250 mL reduced-fat milk presented the best metabolic profile, anthropometric measurements, and GH status.

Table 3
Anthropometric measures and metabolic profile of 203 obese patients according to amount of milk consumption (<250 mL/250 mL/>250 mL).

Parameters	<250 mL	250 mL	>250 mL	*p* value
	71 (25.3%)	77 (27.4%)	55 (19.6%)	
Age (years)	35.1 ± 10.5	37.1 ± 11.2	37.1 ± 14.1	0.369
BMI (kg/m^2)	44.4 (35.2–58.8)	40.4 (35.2–51.9)	43.1 (35.9–54.5)	<**0.001**
Waist circumference (cm)	130.2 ± 17.0	121.9 ± 14.7	126.7 ± 13.2	**0.004**
SBP (mmHg)	130.0 (95.0–160.0)	120.0 (80.0150.0)	130.0 (100.0–160.0)	**0.019**
DBP (mmHg)	80.0 (50.0–110.0)	80.0 (60.0–100.0)	80.0 (60.0–110.0)	**0.015**
Peak GH response (μg/L)	2.7 (0.1–14.8)	6.9 (0.1–18.0)	4.6 (0.1–18.6)	<**0.001**
IGF-1 (μg/L)	140.0 (35.0–270.0)	199.0 (67.0–483.0)	138.0 (50.0–304.0)	<**0.001**
IGF-1 (SDS)	−2.8 (−5.4 to 0.4)	−1.5 (−4.1 to 5.9)	−2.8 (−6.1 to 2.4)	<**0.001**
PTH (pg/ml)	42.0 (16.1–116.0)	44.3 (15.6–109.0)	34.6 (19.0–123.0)	0.117
Total Calcium (mg/dl)	9.5 ± 0.4	9.5 ± 0.4	9.7 ± 0.4	**0.002**
Corrected Calcium (mg/dL)	9.1 ± 0.4	9.0 ± 0.4	9.3 ± 0.3	<**0.001**
Fasting Glucose (mg/dL)	94.0 (61.0–142.0)	85.0 (61.0–243.0)	91.0 (73.0–269.0)	**0.001**
Fasting Insulin (μU/mL)	16.4 (5.0–44.5)	11.2 (4.7–46.3)	14.5 (5.0–58.3)	0.055
HoMA-IR	3.8 (1.1–15.5)	2.4 (0.8–20.9)	3.2 (1.0–38.7)	**0.027**
Creatinine (mg/dL)	0.8 (0.5–1.1)	0.8 (0.5–1.1)	0.7 (0.5–1.2)	0.186
Serum albumin (g/dL)	4.4 ± 0.3	4.5 ± 0.3	4.5 ± 0.3	0.514
Total serum protein (g/dL)	7.7 (6.3–8.6)	7.8 (6.9–8.8)	7.8 (6.3–8.7)	0.865
Total cholesterol (mg/dL)	185.3 ± 43.1	174.8 ± 42.2	185.7 ± 36.2	0.200
HDL cholesterol (mg/dL)	49.0 (31.0–98.0)	51.0 (27.0–75.0)	50.0 (25.0–75.0)	0.977
LDL cholesterol (mg/dL)	103.7 ± 43.8	96.8 ± 44.7	105.4 ± 37.9	0.462
Fasting Triglycerides (mg/dL)	152.0 (63.0–480.0)	126.0 (44.0–583.0)	147.0 (92.0–264.0)	0.064
AST (U/L)	29.0 (7.0–116.0)	27.5 (7.0–91.0)	30.0 (8.0–109.0)	0.550
ALT (U/L)	37.0 (5.0–96.0)	38.5 (6.0–202.0)	33.0 (9.0–199.0)	0.776
γGT (U/L)	34.0 (12.0–95.0)	33.0 (8.0–242.0)	34.0 (11.0–155.0)	0.930
MetS (n, %)	32 (45.7%)	22 (28.6%)	22 (39.3%)	0.105

The best anthropometric measurements and metabolic profile were observed in subgroup of patients consuming a 250 mL of milk. In addition, this subgroup presented the highest peak GH response and IGF-1 SDS. In particular, the peak GH response was sufficient in 71.4% consumers of 250 mL milk *vs* 32.4% and 50.9% consumers of < or >250 mL milk, respectively ($\chi^2 = 22.61$; $p < 0.001$). Results are expressed as mean ± SD or as median plus range according to variable distributions evaluated by Kolmogorov–Smirnov test. Differences between groups were analyzed by ANOVA or Kruskal–Wallis test, when appropriate. The chi square (χ^2) test was used to determine significance differences in frequency distributions of MetS. A *p* value in bold type denotes a significant difference ($p < 0.05$). ***BMI***, body mass index; ***SBP***, systolic blood pressure; ***DBP***, diastolic blood pressure; ***GH***, growth hormone; ***IGF-1***, insulin-like growth factor 1; ***IGF-1*** (***SDS***), insulin-like growth factor 1 standard deviation score; ***PTH***, parathyroid hormone; ***HoMA-IR***, homeostasis model assessment - insulin resistance; ***HDL***, High-density lipoprotein; ***LDL***, low-density lipoprotein; ***AST***, aspartate aminotransferase; ***ALT***, Alanine transaminase; ***γGT***, γ-glutamyltransferase; ***MetS***, metabolic syndrome.

No previous studies have investigated at the same time in obese individuals the milk consumption by the use of prospective 7-days food diary record and the somatotropic axis functional testing, by the use of a dynamic evaluation of GH secretion and IGF-1 levels standardized for age and sex. To the best of our knowledge this is the first study reporting the positive association between milk consumption and somatotropic axis in obesity.

As expected, in our study we found that milk consumption was correlated positively with total calcium and negatively with BMI. The inverse association between calcium intake and body weight was originally described almost 30 years ago, in a study on the relationship between nutrient intake and blood pressure by McCarron et al. [24]. This observation was subsequently confirmed by Trevisan et al. [25] while evaluating the inverse relationship between BMI and the frequency of consumption of milk in Italian male adults. Finally, Zemel et al. [26], by analyzing data from National Health and Nutrition Examination Survey (NHANES) III, demonstrated a profound reduction in the odds of being in the highest quartile of adiposity associated with increases in calcium and dairy product intake.

In addition to being a major source of dietary calcium, milk is rich in specific amino acids that may have strong influence on IGF-1 levels. The primary stimulator of IGF-1 secretion is GH, with a fine modulation by IGF-binding proteins (BP), primarily IGFBP-3 [9]. IGF-1 levels represents also a stable and integrated measurement of GH production and its peripheral effects. However, IGF-1 levels are also nutritionally regulated, with a positive association between milk intake in both childhood and adulthood [27,28]. In particular, both energy and protein are critical to the regulation of serum IGF-1 levels [29]. Data from the European Prospective Investigation into Cancer and Nutrition (EPIC), reported a 2.5% and 2.4% increase in IGF-1 *per* 3% and 2% increase in energy from total protein and dairy, respectively [30]. In addition, IGF-1 contained in cow's milk is structurally identical to human IGF-1; however it is generally believed that the bioactivity of milk-derived IGF-1 is lost because of rapid proteolysis in the upper gut [31]. Thus, the physiologic basis for the positive association between milk intake and circulating IGF-1 levels, especially considering the GH status, remains unclear.

Rich-Edwards et al. [32] found that milk drinking may cause increases in GH levels of prepubertal children. However, considering the pulsatile nature of GH secretion, the assessment of GH secretion requires the use of pharmacological challenges, such GHRH + ARGININE. This test, currently considered the favourite diagnostic tool due to its high specificity and sensitivity, as well as tolerability [33]. GHRH + ARGININE challenge is also the only test for which BMI-dependent variability of GH responsiveness has been investigated [34], with the definition of 4.2 μg/L as the appropriate GH cut-off in adults with BMI ≥30 kg/m^2 [22]. Using this new cut-off value of the GHRH + ARGININE test, about 1/3 morbidly obese individuals, without any evidence of organic pituitary disease, presented a low peak stimulated GH [35]. Of interest, changes in the cardiovascular risk profile and body composition in obese individuals with low GH status are associated with increased cardio-metabolic sequelae [36]. In the present study, the evaluation of GH status allowed us to better define the relationship between milk and somatotropic axis, as we found that milk consumption is positively associated not only with IGF-1 levels, but also with stimulated GH secretion. In addition, the subgroup of obese individuals with the highest intake of milk presented the lowest BMI and best metabolic profile.

Several mechanisms to explain the association between higher milk consumption and lower BMI have been suggested. Possible

Table 4
Anthropometric measures and metabolic profile of 77 obese patients consuming 250 mL milk according to milk type.

Parameters	250 mL low-fat milk	250 mL reduced-fat milk	*p* value
	n = 11 (3.9%)	n = 66 (23.5%)	
Age (years)	38.5 ± 11.0	36.8 ± 11.3	0.636
BMI (kg/m^2)	45.6 (41.5–51.9)	40.1 (35.2–46.7)	<**0.001**
Waist circumference (cm)	133.8 ± 15.3	119.9 ± 13.7	**0.003**
SBP (mmHg)	130.0 (110.0–145.0)	120.0 (80.0–150.0)	<**0.001**
DBP (mmHg)	80.0 (65.0–100.0)	80.0 (60.0–95.0)	<**0.001**
Peak GH response (μg/L)	0.4 (0.1–4.9)	7.9 (0.1–18.0)	<**0.001**
IGF-1 (μg/L)	132.0 (85.0–267.9)	218.5 (67.0–483.0)	<**0.001**
IGF-1 (SDS)	−2.5 (−4.0 to 1.0)	−1.3 (−4.1 to 5.9)	<**0.001**
PTH (pg/mL)	41.3 (31.9–75.9)	44.3 (15.6–109.0)	<**0.001**
Total Calcium (mg/dl)	9.5 ± 0.3	9.5 ± 0.4	0.799
Corrected Calcium (mg/dL)	9.1 ± 0.3	9.0 ± 0.4	0.445
Fasting Glucose (mg/dL)	94.0 (84.0–118.0)	84.0 (61.0–243.0)	<**0.001**
Fasting Insulin (μU/mL)	20.8 (14.4–41.9)	9.7 (4.7–46.3)	<**0.001**
HoMA-IR	4.7 (3.4–8.7)	2.1 (0.8–20.9)	<**0.001**
Creatinine (mg/dL)	0.8 (0.5–1.0)	0.8 (0.5–1.1)	0.178
Serum albumin (g/dL)	4.4 ± 0.3	4.5 ± 0.3	0.211
Total serum protein (g/dL)	7.9 (7.5–8.4)	7.8 (6.9–8.8)	**0.001**
Total cholesterol (mg/dL)	201.1 ± 39.6	170.4 ± 41.3	**0.008**
HDL cholesterol (mg/dL)	41.0 (32.0–59.0)	51.0 (27.0–75.0)	<**0.001**
LDL cholesterol (mg/dL)	127.4 ± 36.9	91.7 ± 44.1	**0.011**
Fasting Triglycerides (mg/dL)	141.0 (53.0–274.0)	124.0 (44.0–583.0)	<**0.001**
AST (U/L)	29.0 (13.0–45.0)	26.5 (7.0–91.0)	<**0.001**
ALT (U/L)	31.5 (13.0–69.0)	40.0 (6.0–202.0)	<**0.001**
γGT (U/L)	39.5 (28.0–93.0)	31.0 (8.0–242.0)	<**0.001**
MetS (n, %)	4 (36.4%)	18 (27.3%)	**0.029**

The subgroup of the consumers of 250 mL reduced-fat milk presented better anthropometric measurements and metabolic profile compared with those consuming 250 mL low-fat milk. In addition, this subgroup presented higher peak GH response and IGF-1 SDS. In particular, the peak GH response was sufficient in 78.8% consumers of 250 mL reduced-fat milk *vs* 27.3% consumers of 250 mL low-fat milk ($\chi^2 = 9.87$; p = 0.002). Results are expressed as mean ± SD or as median plus range according to variable distributions evaluated by Kolmogorov–Smirnov test. *T*-test or Mann–Whitney test were used to test the significance of differences among the two groups. The chi square (χ^2) test was used to determine significance differences in frequency distributions of MetS. A *p* value in bold type denotes a significant difference (p < 0.05). ***BMI***, body mass index; ***SBP***, systolic blood pressure; ***DBP***, diastolic blood pressure; ***GH***, growth hormone; ***IGF-1***, insulin-like growth factor 1; ***IGF-1*** (***SDS***), insulin-like growth factor 1 standard deviation score; ***PTH***, parathyroid hormone; ***HoMA-IR***, homeostasis model assessment - insulin resistance; ***HDL***, High-density lipoprotein; ***LDL***, low-density lipoprotein; ***AST***, aspartate aminotransferase; ***ALT***, Alanine transaminase; ***γGT***, γ-glutamyltransferase; ***MetS***, metabolic syndrome.

mechanisms by which milk may affect energy balance include the well-known satiating effect of milk proteins, the increased faecal fat excretion as well as the calcium appetite concept [37].

Despite the great body of evidence supporting the beneficial effects delivered by the regular consumption of milk, very little is known about the biological mechanisms likely to be involved in the relationships of milk and dairy foods with human health. Milk is likely the most important source of bioavailable calcium, especially when associated to vitamin D. Although fat-reduced milk products tend to have low vitamin D, their vitamin D content is however higher than that in low-fat milk products. Among its beneficial effects, bioavailable calcium has been reported to reduce fat absorption through the forming of soaps in the intestine [38]. The independent positive association of milk consumption, specifically 250 mL reduced-fat milk, with GH status in obese individuals let us to speculate that the preservation of somatotropic axis in obese individuals regularly consuming milk might be one of the mechanisms involved in the protective effects of milk on obesity and obesity-related co-morbidities, likely through the effects of specific milk nutrients, such as amino acids or lipids, on GH physiologic secretion. In particular, amino acids, such as arginine, lysine and ornithine, can stimulate GH release, while FFAs exert an inhibitory control on GH secretion [9,14]. Thus, in this aspect, it is intriguing to hypothesize that 250 mL serving provides the best association between energy intake, fat and protein contents, and amount of calcium and vitamin D.

Limitations of this study warrant some consideration. Firstly, the cross-sectional nature of this study did not allow to determine whether any cause-and-effect relationship exists between milk consumption and GH status. Second, in this study we could not consider the protein for dairy, cheese, and yogurt groups. However, previous studies have reduced the primary role of protein intake in the positive association between milk consumption and IGF-1 [28]. In addition, as the peak GH response was higher among low-fat compared with reduced fat milk consumers, it will be mandatory to verify the association between GH status and fat content in milk also including obese subjects consuming whole fat milk. Third, the detailed nature of 7-days record could induce the misreporting of food intake and portion sizes. However, besides to minimize the subject recall bias, seven days has been shown to be an appropriate length of time to accurately assess nutrient intake and effectively

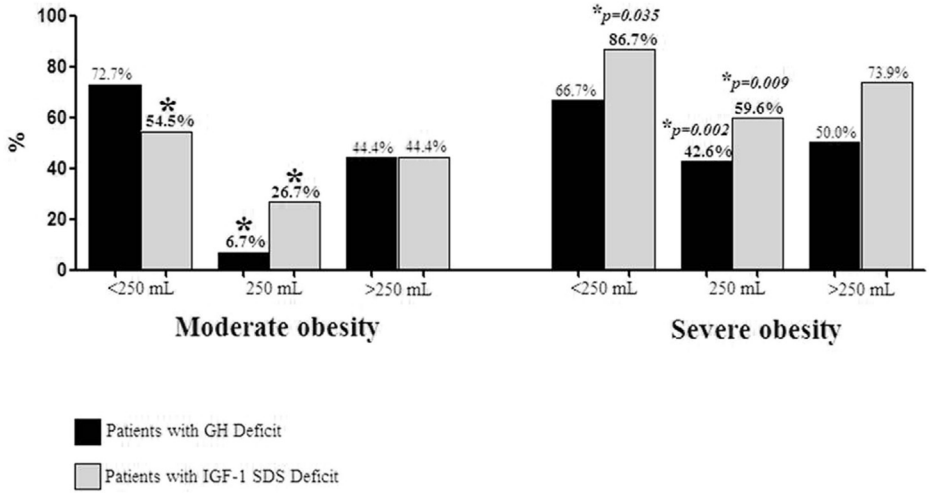

Fig. 2. Different prevalence of growth hormone deficiency (GHD) and insulin-like growth factor (IGF)-1 deficiency according to the amount of milk consumption and degree obesity. The peak GH response and IGF-1 SDS levels in the study population grouped according to the amount of milk consumption and BMI. In both patients with moderate and severe obesity the prevalence of individuals with a normal peak GH response and normal IGF-1 SDS levels were higher among individuals consuming the 250 mL serving of milk compared with those consuming different servings. Results are expressed as percentage. The chi square (χ^2) test was used to determine significance in differences in the frequency distributions of GHD and IGF-1 SDS deficiency, respectively. ***GH***, growth hormone; ***IGF-1*** (***SDS***), insulin-like growth factor-1 standard deviation score; ***BMI***, body mass index.

Table 5
Bivariate proportional odds ratio models performed to assess the association of milk consumption (yes/no) with anthropometric measures and metabolic profile.

Parameters	OR	*p* value	95% IC	AIC	R^2 adj
Gender	1.24	0.462	0.70–2.18	12.74	−0.002
Age (years)	0.99	0.207	0.97–1.00	136.30	0.025
BMI (kg/m^2)	0.73	**<0.001**	0.67–0.79	308.65	0.570
Waist circumference (cm)	0.94	**<0.001**	0.92–0.96	194.51	0.195
SBP (mmHg)	0.96	**<0.001**	0.94–0.98	83.54	0.078
DBP (mmHg)	0.97	**0.017**	0.95–0.99	61.12	0.027
PTH (pg/mL)	0.97	**<0.001**	0.95–0.98	207.28	0.288
Total Calcium (mg/dL)	8.11	**<0.001**	4.06–16.20	120.51	0.203
Corrected Calcium (mg/dL)	3.43	**0.001**	1.74–6.76	179.87	0.163
Fasting Glucose (mg/dL)	0.95	**<0.001**	0.94–0.97	233.68	0.352
Fasting Insulin (μU/mL)	0.90	**<0.001**	0.88–0.93	297.46	0.455
HoMA-IR	0.76	**<0.001**	0.70–0.83	285.61	0.492
Creatinine (mg/dL)	0.30	0.158	0.06–1.60	44.53	0.039
Serum albumin (g/dL)	2.42	0.069	0.92–6.35	59.64	0.014
Total cholesterol (mg/dL)	0.99	**0.003**	0.99–0.99	232.41	0.053
HDL cholesterol (mg/dL)	1.03	**0.023**	1.00–1.05	127.26	−0.027
LDL cholesterol (mg/dL)	0.99	**0.004**	0.99–0.99	304.60	0.055
Fasting Triglycerides (mg/dL)	0.99	**0.035**	0.99–0.99	240.23	0.056
AST (U/L)	0.99	0.061	0.97–1.00	164.40	0.072
ALT (U/L)	0.99	**0.036**	0.98–0.99	182.59	0.044
γGT (U/L)	0.99	**0.019**	0.97–0.99	192.40	0.149
MetS (yes/no)	0.22	**<0.001**	0.12–0.39	41.48	0.099

Bivariate proportional odds ratio model performed to assess the association of milk consumption (yes/no) with anthropometric measures and metabolic profile. As expected, milk consumption was associated with both anthropometric measurements and metabolic profile. A *p* value in bold type denotes a significant difference ($p < 0.05$). ***BMI***, body mass index; ***SBP***, systolic blood pressure; ***DBP***, diastolic blood pressure; ***PTH***, parathyroid hormone; ***HoMA-IR***, homeostasis model assessment - insulin resistance; ***HDL***, High-density lipoprotein; ***LDL***, low-density lipoprotein; ***AST***, aspartate aminotransferase; ***ALT***, Alanine transaminase; ***γGT***, γ-glutamyltransferase; ***OR***, odds ratio; ***AIC***, Akaike Information Criterion; ***IC***, confidence interval.

represents an individual's normal dietary patterns by covering weekdays and weekends [39,40]. Finally, in this study we did not investigate the possible effects of different food products/diet regimen on the association between metabolic profile and milk consumption. In conclusion, although further studies are needed to better define the possible involvement of milk in the fine tuning of the somatotropic axis activity in obesity, overall findings suggest a novel positive association between milk consumption, metabolic profile and GH status in obese individuals.

Table 6
Multivariate proportional odds ratio model, adjusted for BMI, age and gender, to assess the association among three different servings of milk (125/250/375 mL) with the GH status.

	Probability	*p* value	OR
Model 1 (peak GH response)			
125 mL	0.32	0.086	**0.78**
250 mL	0.41	**0.002**	
375 mL	0.25		
Model 2 (IGF-1 SDS)			
125 mL	0.23	**0.026**	**0.41**
250 mL	0.62	0.295	
375 mL	0.17		
Model value fittings			
	Model 1 (peak GH response)	Model 2 (IGF-1 SDS)	
AIC	408.92	421.38	
R^2 adj	0.007	0.006	

Multivariate proportional odds ratio model performed to assess the association among three different servings of milk (125/250/375 mL) with the GH status. A *p* value in bold type denotes a significant difference ($p < 0.05$). After adjusting for BMI, age and gender, the subjects consuming 250 mL presented the best GH status. AIC value fitting and R^2 adjusted for peak GH response are not different, respectively, than the AIC value fitting and R^2 adjusted for IGF-1 SDS, respectively. ***GH***, growth hormone; ***IGF-1*** (***SDS***), insulin-like growth factor 1 standard deviation score; ***OR***, odds ratio; ***AIC***, Akaike Information Criterion; ***IC***, confidence interval.

Table 7
Bivariate proportional odds ratio model, adjusted for BMI, age and gender, to assess the association of milk consumption (yes/no; model 1) and type of milk (reduced-fat/low-fat milk; model 2), with the GH status.

	OR	*p* value	95% IC
Model 1 – Milk consumption			
Peak GH response		**<0.001**	0.105–0.285
Yes	0.60		
No	0.40		
IGF-1 SDS		**<0.001**	0.023–0.659
Yes	0.58		
No	0.42		
Model 2 – Type of milk			
Peak GH response		**<0.001**	0.349–0.621
Reduced-fat	0.60		
Low-fat	0.40		
IGF-1 SDS		**<0.001**	0.534–1.04
Reduced-fat	0.65		
Low-fat	0.35		
Model value fittings			
	Model 1		Model 2
	Peak GH response	IGF-1 SDS	Peak GH response	IGF-1 SDS
AIC	242.82	238.25	173.04	194.17
R^2 adj	0.14	0.13	0.44	0.38

Bivariate proportional odds ratio model performed to assess the association of milk consumption (yes/no; model 1) and type of milk (reduced-fat/low-fat milk; model 2), with the GH status. A *p* value in bold type denotes a significant difference ($p < 0.05$). After adjusting for BMI, age and gender, the subjects consuming milk, in particular reduced-fat milk, have higher peak GH response and IGF-1 SDS than those not consuming milk or consuming low-fat milk. In model 2, the model fitting is better with peak GH response covariate than IGF-1 SDS. AIC value fitting and R^2 adjusted for peak GH response are lower and higher, respectively, than the AIC value fitting and R^2 adjusted for IGF-1 SDS, respectively. ***GH***, growth hormone; ***IGF-1*** (***SDS***), insulin-like growth factor 1 standard deviation score; ***OR***, odds ratio; ***AIC***, Akaike Information Criterion; ***IC***, confidence interval.

Regardless of the pathogenetic mechanisms, this novel association might be relevant in a context where obese individuals commonly skip breakfast, and to drink milk is often discourage by its saturated fat contents. The association between milk consumption and GH status suggests that a growing cooperation between Nutritionists and Endocrinologists might provide a combination key in the complex management of the obese patients and may encourage further studies to evaluate the effects of the

Table 8
Bivariate proportional odds ratio model, adjusted for BMI, age and gender, to assess the association of 250 mL reduced-fat or 250 mL low-fat.

	OR	*p* value	95% IC
Peak GH response			0.327–1.610
250 mL reduced-fat milk	0.54	**0.003**	
250 mL low-fat milk	0.46	0.252	
Proportional odds	0.83		
IGF-1 SDS			−0.130 to 0.015
250 mL reduced-fat milk	0.63	**<0.001**	
250 mL low-fat milk	0.36	0.100	
Proportional odds	0.57		
Model value fittings			
	Peak GH response		IGF-1 SDS
AIC	358.82		344.38
R^2 adj	0.21		0.26

Bivariate proportional odds ratio model performed to assess the association of 250 mL reduced-fat or 250 mL low-fat. A *p* value in bold type denotes a significant difference ($p < 0.05$). After adjusting for BMI, age and gender, subjects consuming 250 mL reduced-fat milk have higher peak GH response and IGF-1 SDS than those consuming 250 mL low-fat milk. AIC value fitting and R^2 adjusted for peak GH response are not different, respectively, than the AIC value fitting and R^2 adjusted for IGF-1 SDS, respectively. ***GH***, growth hormone; ***IGF-1*** (***SDS***), insulin-like growth factor 1 standard deviation score; ***OR***, odds ratio; ***AIC***, Akaike Information Criterion; ***IC***, confidence interval.

changes in milk intake on body weight and somatotropic axis in obesity.

Authors' contributions

The authors' responsibilities were as follows LB and SS: were responsible for the concept and design of the study and interpreted data and drafted the manuscript.

LB, SS and CDS: conducted statistical analyses; PEM and AC: provided a critical review of the manuscript.

All authors contributed to and agreed on the final version of the manuscript.

Conflict of interest

None of the authors had a conflict of interest.

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