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Maternal metabolic syndrome and selenium: Endocrine energy balance during early programming

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ABSTRACT

Background: Maternal metabolic syndrome during gestation and lactation leads to several Se-status-related metabolic changes in offspring. MS leads to hepatomegaly, liver oxidation, resistance to insulin challenges and selenoptroteins expression upregulation, producing an energy imbalance in hepatocytes. As Se is necessary for correct heart function, Se deposits are depleted and selenoproteins expression downregulated in heart; this depletion being related to cardiovascular damage. Recently, selenoproteins have been directly implicated in the central endocrine regulation of appetite and energy homeostasis.

Methods: To obtain information about how Se is involved in regulating endocrine peripheral energy balance during MS process, two experimental groups of dam rats were used: control (Se: 0.1 ppm) and MS (Fructose 65% and Se: 0.1 ppm). At the end of lactation (21d old), the pups' appetite profile, tissular Se deposits and peptides from gastrointestinal tract (including pancreas), leptin, skeletal growth markers and cytokines in serum were measured.

Results: MS-exposed pups present changes in Se homeostasis, appetite profile and endocrine energy balance signals related to impaired insulin secretion and high leptin serum values. This profoundly affects the pups' growth profile since muscle and bones are in catabolic process and brown adipose tissue (BAT) mass decreases.

Conclusion: These results indicate that the pups are suffering a process similar to diabetes type 1 which appeared when dams received low Se dietary supply and they point to Se as an important marker and key treatment for these disorders during gestation and lactation that affect future adult health.

1. Introduction

Endocrine metabolic disorders, such as metabolic syndrome (MS), affect both mother and offspring by altering their metabolic fetal programming [1–3]. The prevalence of MS is increasing worldwide [4]; it appears in 25% of pregnant women [5] and the pediatric age group is greatly affected [6]. MS is defined as a cluster of anthropometric, physiological and biochemical abnormalities that predispose affected individuals to developing insulin resistance (IR), diabetes (DM) and cardiovascular disease (CVD) [7].

Recently, MS has been related to changes in Se homeostasis. Se forms part of different selenoproteins such as the glutathione peroxidase (GPx) family of antioxidant enzymes and the Se plasma transporter selenoprotein P (SelP). These selenoproteins are related to IR and MS by their actions in modulating reactive oxygen species (ROS) signals in the insulin signaling process and the activation of the energy status sensor adenosine monophosphate-activated protein kinase (AMPK) in liver [8]. However, both infra- and supra- dietary Se interventions have been involved in the development of IR and metabolic imbalance [9–12]. Using infra- and supra- Se dietary protocols in dams, Ojeda et al. [13] have described that offspring exposed to an Se-supplemented diet during gestation and lactation (early programming) present IR, obesity, hepatomegaly and a metabolic profile similar to those offspring whose mothers suffer type 2 diabetes (DM2). However, pups exposed to a low Se diet present a metabolic profile more similar to type 1 diabetes (DM1), with extremely low insulin secretion and energy expenditure profiles.

In an experimental high-fructose-diet-induced MS rat model that has been used previously by this research group, Se body distribution and selenoprotein activities have been found to be up- and down-regulated in different tissues taken from both dams and their offspring [3,14]. This makes understanding whether Se supplementation could be an effective therapy for MS development or a risk a difficult task. In the liver of MS pups there is an increase in Se deposits together with hepatomegaly, oxidation, resistance to insulin challenges and upregulation in selenoproteins expression [15]. However, in the heart of pups

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exposed to the same MS protocol, Se deposits are depleted and selenoproteins expression downregulated. Since Se is necessary for a correct heart function, avoiding mitochondrial oxidation and apoptosis, this depletion of Se deposits is related to cardiovascular damage in the pups [16]. Selenoproteins have also been recently implicated in the central endocrine regulation of appetite and energy homeostasis, since GPxs modulate ROS and endoplasmatic reticulum (ER) stress production in the hypothalamic arcuate nucleus (ARC), preventing this latter's malfunction [17].

The endocrine energy balance system provides the hypothalamus with information from peripheral signals such as nutrients and hormones. The hypothalamus then integrates the information and regulates appetite and energy expenditure, mainly by two neural populations in the ARC nucleus: first are the NPY/AgRP neurons which, having orexigenic functions, increase appetite and decrease energy expenditure. The second are the POMC/CART neurons which, having anorexigenic functions, decrease appetite and increase energy expenditure [18]. Peripheral endocrine signals are divided into long-term endocrine energy balance signals and short-term energy balance signals. The first gives information about the energy stored, mainly via leptin and insulin, which directly stimulate POMC/CART neurons and inhibit NPY/AgRP neurons leading to anorexigenic effects. Insulin and leptin are secreted in proportion to the size of the existing fat mass from pancreas and adipose tissue, respectively. The short-term signals are composed of the neuroendocrine signals from stomach (Ghrelin) and the gastrointestinal tract (GIT) (glucagon-like peptide-1 (GLP-1), glucagon-like insulinotropic peptide (GIP) and peptide YY (PYY)) including pancreas (pancreatic polypeptide (PP) and Amilyn). These send information to the hindbrain and have anorexigenic effects via vagus, except Ghrelin which directly inhibits POMC/CART neurons having orexigenic actions, providing information about the food that is eaten and by how much the stomach is distended [19–21].

The aim of the present study is to continue analyzing the repercussion of Se status in MS fetal programming via long- and short-term endocrine peripheral signals related to appetite and energy balance.

2. Material and methods

2.1. Animals

Male and female Wistar rats (Centre of Production and Animal experimentation, Vice-rector's Office for Scientific Research, University of Seville) weighing approximately 150–200 g, were randomised into two groups: control (C), metabolic syndrome (MS). Animal care procedures and experimental protocols were performed in accordance with EU regulations (Council Directive 86/609/EEC, November 24th 1986) and approved by the Ethics Committee of the University of Seville. All rats received drinking water and diet ad libitum during three week before mate, and then, during gestation (3 weeks) and lactation (3 weeks) periods. MS group was feed with rich fructose diet (65%) to induce MS which contained 0.1 ppm of Se while C group received basic solid diets with 0.1 ppm of Se (Se was added to both diets in the form of anhydrous sodium selenite (an inorganic compound; Panreac, Barcelona, Spain)). The diets of these rats were prepared according to The Council of the Institute of Laboratory Animal Resources (ILAR, 1979) which details known nutrient requirements for most of the common laboratory animals.

In four week, male (n = 3) and female (n = 6) rats were mated to obtain the first-generation offspring for each group. Pregnant female rats were inspected daily by the presence of the vaginal plug, which indicated day zero of pregnancy; at this moment pregnant rats were housed individually in plastic cages. The day of parturition, which occurs spontaneously three weeks after coitus, was designated as day 1 of lactation. The offspring number was reduced to 8 per mother at parturition (four males and four females, when this was possible). The experiments were performed on the offspring of all groups to 21d postpartum. In this study, we have used 8 pups per group to measure all the parameters cited below. These 8 pups represent all the litters, as a maximum of 2 rats per litter, and were allocated to each group taking into account the sex.

2.2. Nutritional controls

Body weights of the dam rats were determined once a week while that the amount of food and liquid consumed by rats were monitored daily until the end of the experimental period. Se intake was calculated by multiplying the food consumed by ppm of Se in the diets. Weekly, body weight and cranium-caudal length of pups was controlled, using a metric calliper, until end of the experimental period. All measures were taken at 9:00 a.m. to avoid changes due to circadian rhythms.

2.3. Samples

The amount of milk consumed by the offspring at the end of the lactation period (days 19 and 20) was estimated by subtracting the weight of the pups obtained immediately prior to returning them to the dam from their weight after 30 min of suckling. In order to obtain the maximum amount of milk at day 21 of lactation, 3 h after removing the litters from their mothers, the dams were anesthetized with urethane, and milk samples were immediately collected. The milk was obtained by gently massaging the area around each of the 12 mammary glands and then pressing upward from the base of the gland towards the nipple. The amount of milk collected was around 1 to 1.5 ml per dam.

At the end of the experimental period, dams and their pups were weighed and anesthetized with intraperitoneal 28% w/v urethane (0.5 ml/100 g of body weight). Blood samples were obtained by heart puncture and collected in tubes. The serum was prepared using low-speed centrifugation for 15 min. at 1300 $\times g$. The abdomen was opened by a midline incision and pancreas, brown and white adipose tissue (BAT and WAT, respectively) and muscle were removed, weighed and stored at −80 °C prior to biochemical determinations. Somatic index of pancreas, BAT and WAT (PIS, BATSI and WATSI, respectively) were calculated as (organ weight/total body weight). BAT/WAT ratio was calculated as (BAT weight/WAT weight).

2.4. Selenium analysis

Selenium levels were determined by graphite-furnace atomic absorption spectrometry, using a PerkinElmer AAnalyst™ 800 high-performance atomic absorption spectrometer with WinLab32 for AA software, equipped with a Transversely Heated Graphite Furnace (THGA) with longitudinal Zeeman-effect background corrector and an AS-furnace autosampler (PerkinElmer, Überlingen, Germany). The source of radiation was a Se electrodeless discharge lamp (EDL). The instrumental operating conditions and the reagents are the same that we have used in the previous paper Ojeda et al. [22]. Samples: serum samples were diluted fivefold in 0.2% v/v HNO_3 and 0.2% Triton X-100 solutions. After 72 h at 100 °C dry temperature, pancreas, muscle and milk samples were weighed and digested in a sand bath heater (OVAN, Badalona, Spain) with nitric acid for 72 h, and perchloric acid and chlorhydric acid (6 N) were added.

2.5. Serum markers of endocrine energy balance

Pancreatic hormones such as C-Peptide, glucagon, insulin, amylin, PP, and the exocrine amylase, ghrelin, leptin and the GIT hormones: GIP, GLP-1, and PYY, TSH and thyroid hormones, ACTH, OPG, PTH and the inflammatory markers: TNF-α, IL-6 and MCP-1 were measured by the Luminex xMAP (Millipore, Darmstadt, Germany). Ghrelin serum levels could not be detected in 21-day-old pups by the Luminex technic used. The homeostatic model for assessment of β-cell function was

Table 1
Nutritional parameters in dams and pups at end of lactation. The results are expressed as mean ± SEM and analysed by Student's *t*-test. The number of animals in each group is 6 and 8 for dams and offspring, respectively. Statistic difference between groups was expressed as p value: C vs MS: *p < 0.05, **p < 0.01, ***p < 0.001.

		C	MS
DAMS	Solid Kcal intake (Kcal/day)	179.7 ± 11.8	145.7 ± 9.3*
	Se intake (μg/day)	4.5 ± 0.3	3.5 ± 0.2*
	Weight gain (g)	50.4 ± 2.9	42.3 ± 2.1*
	Se in serum (ng/mL)	290.2 ± 9.7	283.5 ± 8.3
OFFSPRING	Se in milk (ng/mL)	0.265 ± 0.011	0.261 ± 0.008
	Milk intake (μg/30 min sucklig)	0.51 ± 0.03	0.39 ± 0.03**
	Se intake by milk (μg/30 min sucklig)	0.132 ± 0.002	0.102 ± 0.003**
	Weight gain (g)	26.8 ± 0.7	18.3 ± 0.5***
	Se in serum (ng/mL)	137.1 ± 5.2	136.5 ± 6.3

calculated using the formula: (Fasting insulin serum concentration X 360) / (Fasting glucose concentration - 63). Glucose and triglycerides (TGs) levels were determined using test strips Accutrend (Roche, Spain) from tail blood.

2.6. Statistical analysis

The results are expressed as means ± standard error of the mean (SEM). The data were analysed using a statistical program (GraphPad InStat 3, CA, USA). Student's *t*-test was used to compare the difference between two experimental groups (C and MS), considering statistically significant differences at $p < 0.05$. The Kolmogorov–Smirnov test was used to validate the assumption of normality.

3. Results

3.1. Appetite and body weight

Table 1 shows that dams exposed to MS intake less kcal and Se than control ones, presenting lower increase in body weight. However, serum and milk Se levels were unaltered. MS offspring intake less milk and Se by milk having lower body weight but normal serum Se values.

3.2. Pancreas development: endocrine and exocrine function

Fig. 1 shows that the somatic index of pancreas was decreased in MS pups, which also presented a low β-cell function parameter and serum insulin levels. However, these pups have replete their Se pancreatic deposits and present high serum glucagon values.

3.3. Gastrointestinal tract endocrine function

MS pups have extremely significant low serum GIP and PYY levels, and significantly high serum GLP-1 values (Fig. 2).

3.4. Adipose tissue endocrine function: WAT, BAT, serum TG and leptin

Fig. 3 shows that BAT relative weight was significant decreased in MS pups, which also have a low BAT/WAT ratio. Serum leptin and TGs levels were increased in these pups.

3.5. Skeletal growth: endocrine markers

MS pups have significantly reduced their cranium-caudal length and increased their serum ACTH and PTH levels (Fig. 4).

3.6. Muscle development: selenium, inflammation and creatinine

Fig. 5 shows that MS pups have underdeveloped muscle with extremely low Se deposits and significantly high serum creatinine and IL-6 values.

4. Discussion

The dams which suffered MS induced by a high-fructose diet during gestation and lactation have a lower appetite and lower body weight gain. They intake less food and therefore, among other nutrients, they intake less Se. Interestingly, the dams make an effort to supply a sufficient amount of Se through milk, probably by depleting Se deposits in other tissues such as heart [3] and thus avoid decreasing the amount of Se in serum and milk. Despite this tendency, MS pups have lower appetite and intake lower amount of Se by milk; their serum Se levels were, however, unaltered. It is important to point out that although these animals have repleted their Se pancreatic deposits, they have extremely low Se deposits in muscle. Depending on the tissue's oxidative status and/or tissue Se consumption, they probably redistribute their tissular Se deposits from one tissue to others. For instance, this up- and down-regulation of Se deposits also happens in the liver and heart of MS pups, respectively [15,16]. It is clear that tissular Se homeostasis is altered in MS pups, but even more relevantly, Se dietary intake decreases. Se is a trace element necessary for normal growth and development; it is involved in insulin-like growth factor-I (IGF-1) regulation, correct thyroid hormones synthesis and correct oxidative balance [23]. It is also necessary for endocrine regulation of appetite and energy homeostasis [24]. In this context MS pups intake less Se, have lower appetite and present growth retardation.

Together with leptin, insulin is one of the most important peripheral endocrine signals of the long-term endocrine signals for energy balance. Insulin is synthetized in pancreatic endocrine β-cells and it provides information about the energy stored. An adequate Se supply is necessary for insulin synthesis in order to increase GPx antioxidant activity, thus avoiding pancreatic β-cells oxidation [25]. Pancreatic β-cells have an inherent deficiency in their capacity to cope with oxidative stress and they produce a large amount of ROS during insulin synthesis. For this reason some authors defend that the mass of β-cells declines with the progression of DM2 and ROS production towards DM1 [26]. However, despite the fact that MS pups have increased their Se pancreatic deposits, the repletion is insufficient to ensure a correct pancreatic endocrine function. They have an underdeveloped pancreas with a decrease in β-cell function and drastically low insulin secretion, leading to a pancreatic profile similar to that of DM1.

In an attempt to increase insulin secretion, MS pups have higher levels of two insulin secretion stimulators: glucagon and GLP-1. GLP-1. Together with GIP are incretin gut hormones described as peptides which increase the insulin glucose response triggered by oral glucose administration [27]. Again, this action is insufficient, since serum insulin levels are low. GLP-1 also has a satiety-promoting quality. Previous studies have determined that fructose significantly stimulates GLP-1 secretion in mice, rats and humans [28]. However, in this study as in others, the secretion of the other incretin hormone, GIP, is lower in MS pups. GIP also has lipid-depositing effects, causing a dose-dependent increase in lipoprotein lipase activity and the accumulation of fatty acids and fat deposition [29]. The loss of its function is related to an increase in serum triglycerides (TGs) levels and weight loss [30]. The same occurs in the MS pups studied which have a lower body weight, low GIP serum values and high serum TGs levels. It was recently reported that GIP and GLP-1 are also expressed in pancreatic islets. GIP is secreted from β-cells, which are down-regulated in our MS pups and glucagon and GLP-1 are produced from the same precursor as glucagon in pancreatic α-cells [30]. Since both are higher in the MS pups of this study, α-cells are probably not affected by high fructose exposure. For some reason, the MS model used mainly affects pancreatic β-cells

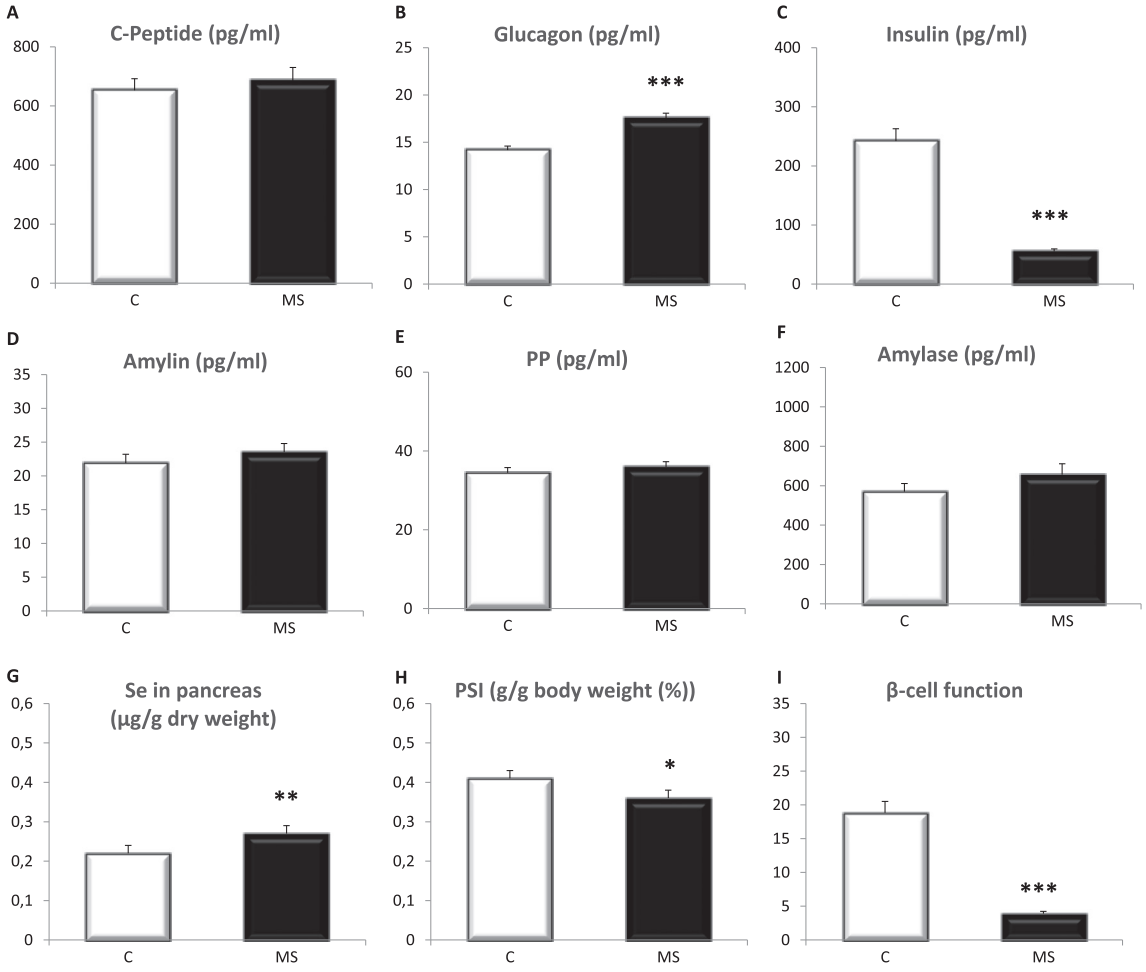

Fig. 1. Pancreas development: endocrine and exocrine function: serum endocrine pancreatic signals, and exocrine serum amylase levels. A: C-Peptide; B: Glucagon; C: Insulin; D: Amylin; E: Pancreatic polypeptide; F: Amylase; G: Se in pancreas: H: PSI = (Pancreas weight/Body weight); I: β-Cell function. The results are expressed as mean ± SEM and analysed by Student's *t*-test. The number of animals in each group is 8. Statistic difference between groups was expressed as p value: C vs MS: *p < 0.05, **p < 0.01, ***p < 0.001.

population. However, since serum amylase levels are unaltered, exocrine pancreas and α-cells populations are not affected.

PYY, the other GIT hormone studied, is also significantly lower in MS pups. This peptide is produced by entero-endocrine L-cells throughout the GIT. PYY inhibits GIT secretion, gut motility and gastric emptying; its secretion is proportional to the caloric content of food. Its peripheral levels are related to food intake in rodents, since it acts directly on ARC nucleus and moreover, it activates BAT depositions [18]. The same effects appeared in this study related to MS pups, since this peptide is lower and they present higher serum TGs levels, lower body weight and low BAT depositions. Curiously, pups exposed to an Se-restricted diet during gestation and lactation also present low serum GIT endocrines signals such as PYY and GIP [31] – like MS pups.

With respect to adipose tissue, MS pups present a low amount of BAT (adipose tissue that dissipates chemical energy as heat via high levels of uncoupling protein 1 and combats hypothermia and obesity by burning lipid) and unaltered WAT (adipose tissue with a high energy storage capacity in the form of TGs) deposits, leading to an anabolic

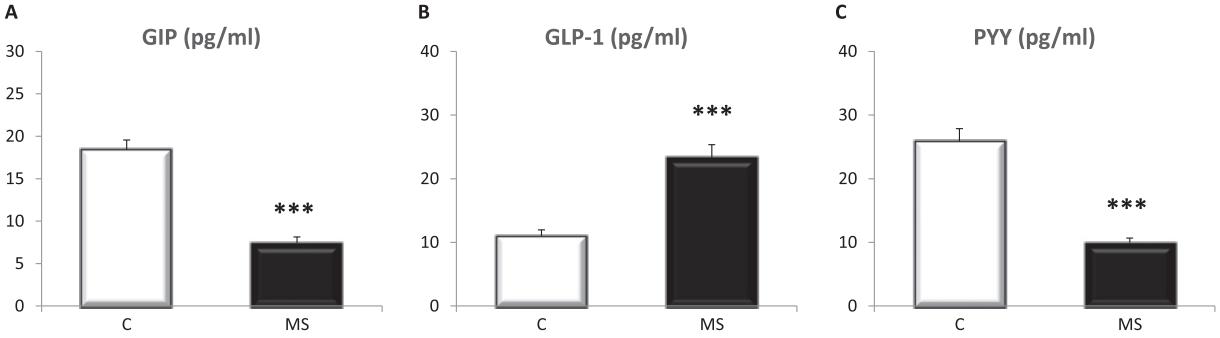

Fig. 2. Serum gastrointestinal tract hormones levels. A: GIP (glucagon-like insulinotropic peptide); B: GLP-1 (glucagon-like peptide-1); C: PYY: YY polypeptide. N = 8. The results are expressed as mean ± SEM and analysed by Student's *t*-test. The number of animals in each group is 8. Statistic difference between groups was expressed as p value: C vs MS: ***p < 0.001.

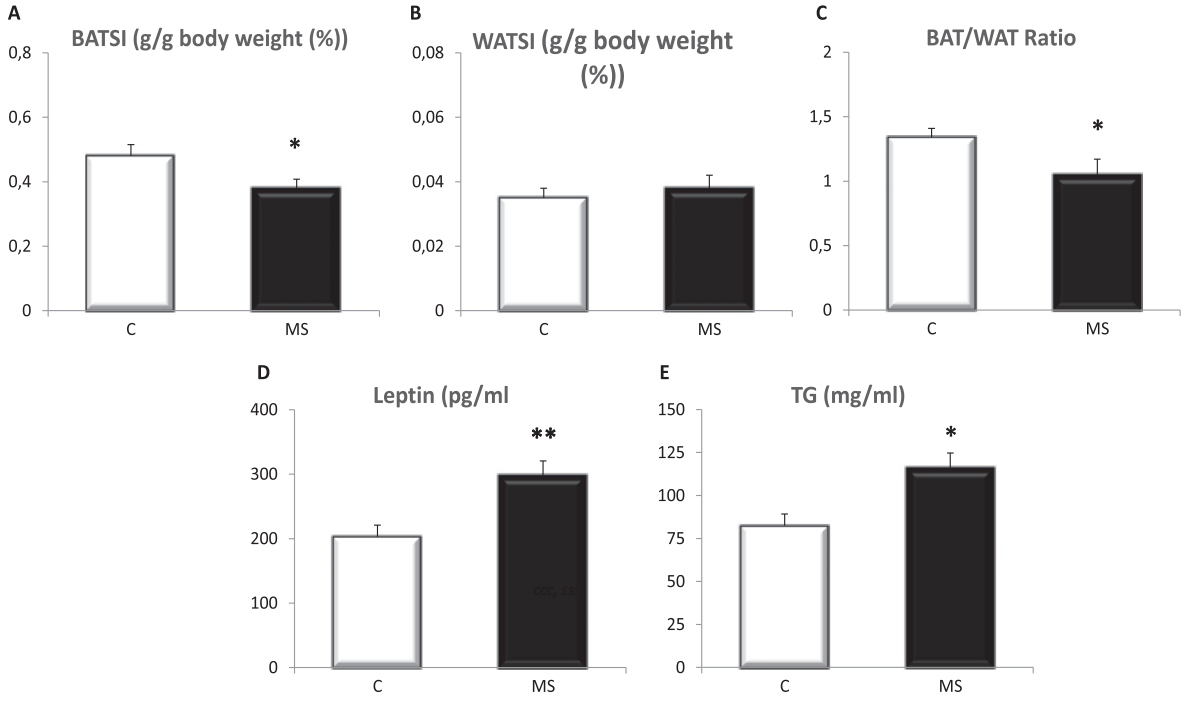

Fig. 3. Serum leptin values and white and brown adipose tissue. A: BATSI = (Brown adipose tissue (BAT) weight/Body weight); B: WATSI = (White adipose tissue (WAT) weight/Body weight); C: BAT/WAT ratio; D: Leptin; E: TG (Triglycerides). The results are expressed as mean ± SEM and analysed by Student's *t*-test. The number of animals in each group is 8. Statistic difference between groups was expressed as p value: C vs MS: *p < 0.05, **p < 0.01.

adipose ratio [32]. This result is strange, since the fact that in adult humans amount of BAT is inversely correlated with body-mass index (BMI), suggesting a potential role of BAT in metabolism [33]. At the end of lactation, the MS pups used in this study have a significantly lower BMI than control ones (2.35 ± 0.05 vs 2.66 ± 0.04). However, this research group has previously found that at birth these MS pups' BMI was significantly higher, having a greater body weight and shorter length than control pups [3]. Since BAT clusters exist principally during

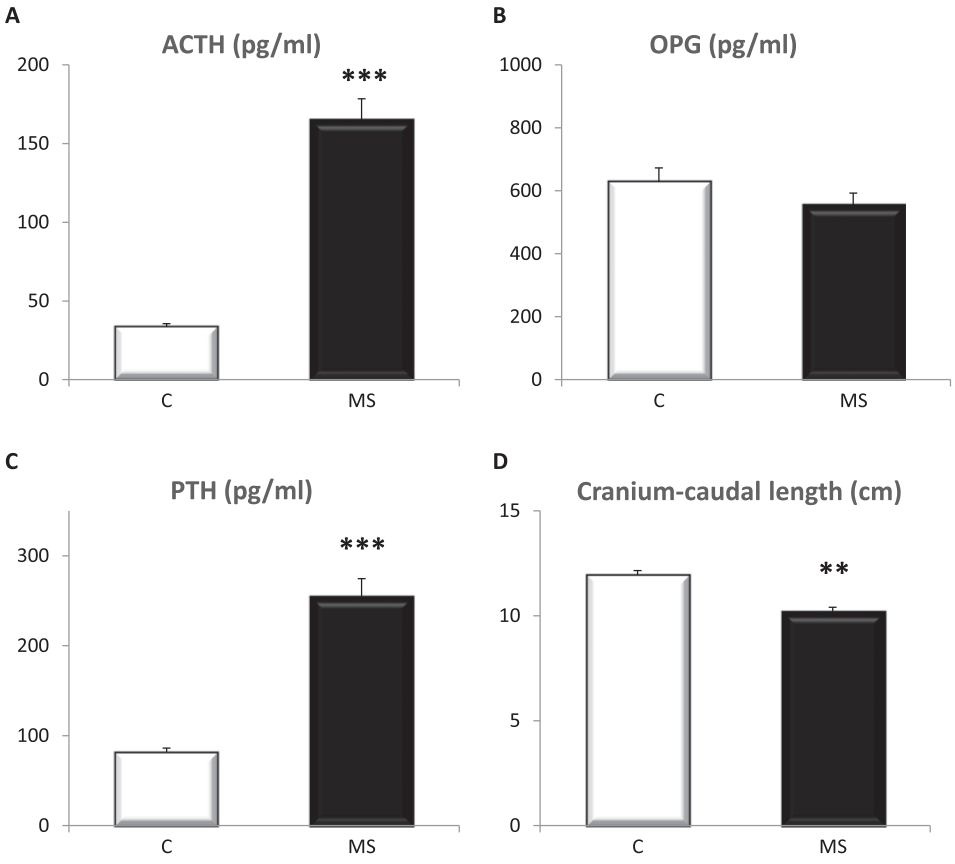

Fig. 4. Skeletal growth and serum hormones related with skeletal development. A: ACTH; B: OPG; C: PTH; D: Cranium-caudal length. The results are expressed as mean ± SEM and analysed by Student's *t*-test. The number of animals in each group is 8. Statistic difference between groups was expressed as p value: C vs MS: **p < 0.01, ***p < 0.001.

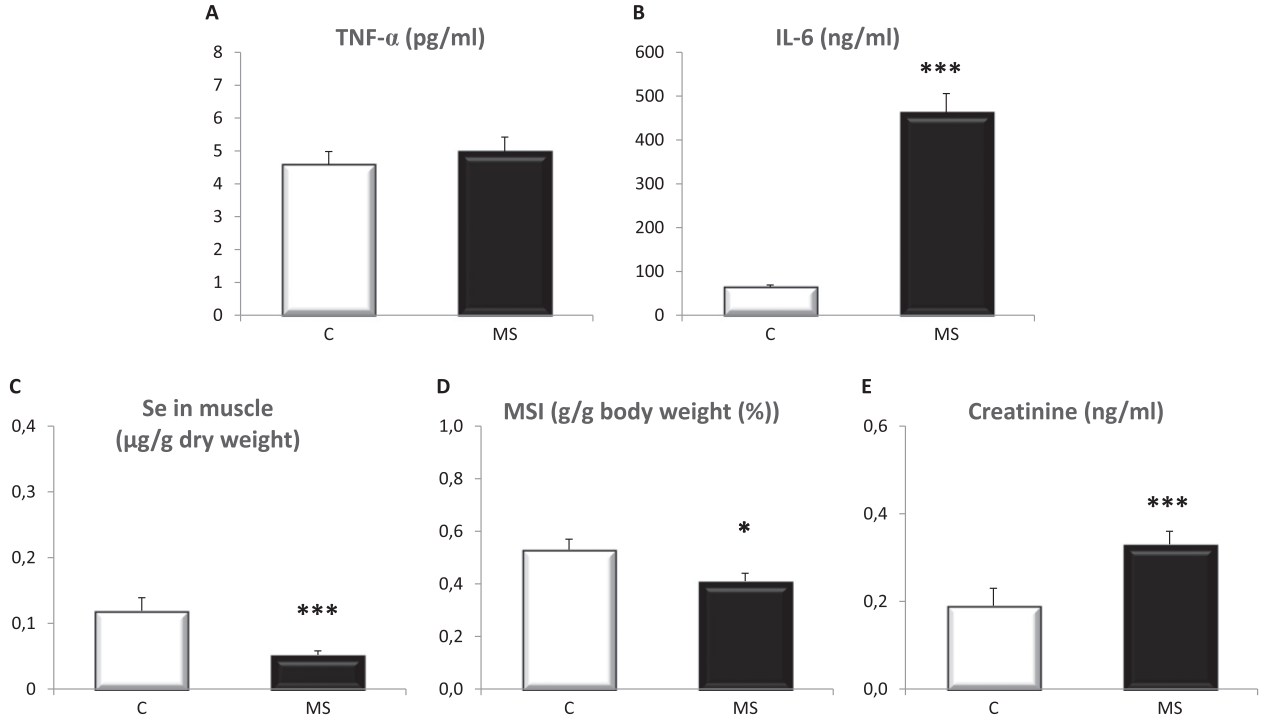

Fig. 5. Muscle development: serum cytokines and creatinine values. A: TNF-α; B: IL-6; C: Se in muscle; D: MSI = (Muscle weight/Body weight); E: Creatinine. The results are expressed as mean ± SEM and analysed by Student's *t*-test. The number of animals in each group is 8. Statistic difference between groups was expressed as p value: C vs MS: *p < 0.05, **p < 0.01, ***p < 0.001.

fetal and neonatal development, and since during this period MS embryos have a high BMI, they also probably have low BAT deposits, which the lactating pups have inherited. In fact, it has recently been shown that intrauterine hyperglycemia is associated with increased DNA methylation of the BAT-specific genes in offspring, leading to BAT development retardation [34]. It has been suggested that adipose tissue plays an important role in linking poor fetal growth and the late development of adult metabolic diseases [35]. BAT transplantation has been described in this context as correcting metabolic phenotypes and improving DM1 and high-fat-diet-induced IR [36,37]. Despite MS pups having a normal amount of WAT, one of this latter's main energy endocrine signals – leptin – is significantly higher in serum. MS pups, however, appear to develop peripheral leptin resistance. These pups have hepatic steatosis [15], low insulin secretion, low BAT deposits and underdeveloped muscle and bone mass - all processes that leptin prevents [38]. Many studies have shown that a high-fructose diet leads to leptin resistance [39–42]. This leptin resistance could be due to intracellular deficits in cell signaling [43], a lower expression of leptin receptors and impaired autophagy in WAT which leads to lower adipose tissue lipid storage capacity [44]. Moreover, it is known that long-term fructose consumption stimulates leptin production by gastric mucosa [45] and that leptin increases GLUT-5 fructose transport activity [46], stimulating fructose uptake. There appears to be a direct relationship between fructose and leptin [47]. Surprisingly, pups exposed to an Se-restricted diet during gestation and lactation also have high serum leptin levels and leptin resistance [30].

In terms of Se levels, in studies with high fat diets and high sucrose diet, an important decrease in GPx4 hypothalamic levels, related to higher oxidative stress [48] has been described. This is also related to a decrease in the number of POMC neurons, along with diminished responsiveness to leptin [49]. It is well-established that one cause of hypothalamic leptin resistance is ER stress and that ROS promotes ER stress [50]. Authors have concluded from these results that not only is selenoproteins synthesis in the pancreas necessary for normal sensitivity to leptin and insulin, but selenoproteins synthesis in the hypothalamus is also necessary.

MS pups have very high PTH serum levels. PTH stimulates osteoclast formation, bone destruction and hypercalcemia, which is in concordance with the lower cranium-caudal length found in MS pups. It is also known that excessive fructose intake causes 1-25(OH)(2)D(3)-dependent inhibition of intestinal and renal calcium transport in growing rats [51]. This could explain the fact that MS pups have an extremely high PTH serum level in order to maintain high serum calcium levels. The other endocrine signal related to skeletal development, osteopontin (OPG), is not significantly altered and therefore bone resorption is not affected. Leptin is a potent OPG inducer and since OPG is not affected in MS pups, it could be deduced that a leptin resistance process is taking place [52]. Reinforcing this idea, leptin is also implicated in normal bone growth, maturation and turnover [53]. MS pups, however, have a short length. Leptin is closely related to the hypothalamus-pituitary-adrenal (HPA) axis by inhibiting it [54]. In MS there are high serum leptin and ACTH levels, implying that a central leptin resistance process is taking place. Chanoine et al. [55] defend that Se levels are related to oxidative stress and alter the leptin-ACTH relationship. The high ACTH levels probably lead to high corticosterone levels which contribute to a general catabolic process. Similar, but more exacerbated, results of these growth markers have been shown in pups exposed to a low-Se diet during gestation and lactation [30], since Se plays a key role in bone health related to antioxidant protection and to regulating bone cell proliferation/differentiation [23].

Another important insulin and leptin resistance-related mechanism is the inflammatory process [56,57]. Serum TNF-α levels are not higher, however, even though, MS pups have higher serum Il-6 levels. Perhaps the increase in IL-6 is related to muscle function, since it is already known that IL-6 is a muscle-produced myokine whose function is to mobilize extracellular substrates and its synthesis is completely independent of TNF-α levels [58]. Given that SM offspring appear to be suffering from a catabolic process and that they have a lower muscular mass, their muscles might be secreting IL-6 into the bloodstream. It would appear that IL-6 from muscle plays a role in the anti-

inflammatory process. The low Se deposits found in muscle are probably related to low muscular development, since Se deficiency causes muscular oxidation and apoptosis in muscle cells, thus decreasing their viability [59]. Moreover, muscles are in a catabolic process since serum creatinine – a waste product of muscle metabolism – levels increase. It is important to take into account that a high level of serum creatinine is used as a marker of renal damage and that MS pups could also be suffering renal damage. Se-deficient pups have high serum creatinine levels and suffer a profound catabolic process [13].

In conclusion, short- and long-term endocrine signals for energy balance are profoundly altered in MS pups, which are developing an insulin disruption similar to DM1 with leptin resistance, growth retardation and BAT, bone and muscle mass destruction. It is also clear that Se homeostasis and tissue deposits are unbalanced and that this trace element is essential during early programming (gestation and lactation) with regard to the endocrine regulation of energy balance and growth. Since Se deposits are up- or down-regulated in different tissues of MS pups, it is important to compare the general energy balance in MS pups with those exposed to high or low Se supply in order to decide on Se supplementation or not. When dams received excessive Se supplementation, a metabolic alteration similar to DM2 appeared in their pups; when dams received a low dietary Se supply, their pups suffered a metabolic alteration similar to DM1 with leptin resistance, growth retardation and an energy-wasting process. MS offspring present a profile that is more similar to the profile of Se-deficient pups, but is not so marked. Controlled Se supplementation should, therefore, be taken into account if, during early programming, there are suspicions of endocrine energy balance dysfunctions, such as MS. These results point to Se as an important marker and treatment during gestation and lactation for these disorders which affect future adult health.

Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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