

Nutrition, obesity and hormones

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Abstract

Obesity is a chronic pathological condition with a multifactorial aetiology, characterised by an excessive body fat accumulation with multiple organ-specific consequences. Emerging evidence highlights that obesity appears to be associated with multiple alterations in the endocrine system. However, the mechanisms underlying the interactions between obesity and this system remain still controversial. This review discusses the impact of obesity on various endocrine systems and, in particular, would provide a general overview on the biochemical changes that may occur in each of these axes in association with obesity.

Introduction

Obesity is a chronic pathological condition with a multifactorial aetiology which comprises genetics, environment, metabolism, lifestyle, and behavioral components.¹⁻³ Complex interac-

tions between genetic and environmental factors which give rise to alterations of the endocrine and metabolic functions have been suggested to contribute to the pathogenesis of this disease.³ As these alterations are secondary, they may be often reversible following body weight loss. Therefore, these effects should be distinguished from those primary endocrine-metabolic disorders that, although uncommon, may foster the development of obesity. On the other hand, informations about those complications affecting the endocrine organs which occur in obese patients as a result of the accumulation of dysfunctional adipocytes also in ectopic sites, such as omental fat, pericardial and peri-renal fat are actually scanty⁴. However they can act as amplifiers of metabolic effects thus worsening the cardiometabolic risk factors in these subjects.⁴

Growth hormone metabolism and obesity

Recent evidence indicates that a functional decreased secretion of somatotropin or growth hormone (GH) in obese subjects appears to be due to specific central mechanisms,^{5,6} such as an increase of the somatostatinergic tone, and/or to peripheral mechanisms such as increased circulating levels of insulin and free fatty acids (FFA).⁷ Furthermore, the reduction of the lipolytic and anabolic effects on muscles exerted by GH and its peripheral mediator, namely the insulin-like growth factor-1 (IGF-1), may further influence the accumulation of visceral fat and may also account for the related metabolic consequences. GH is a protein of 191 amino acids whose secretion from the pituitary is regulated by the hypothalamus. The neuroendocrine control of GH secretion is under the regulation of two neuropeptides, namely GH releasing hormone (GHRH) which stimulates GH secretion, and somatostatin (SS) which inhibits GH secretion. These molecules are produced in the neurons of the arcuate nucleus and ventromedial nucleus of the hypothalamus and in those of anterior periventricular nucleus respectively. GHRH and SS secretion are, in turn, regulated by central neurotransmitters, such as dopamine, adrenaline, noradrenaline, serotonin, histamine and gamma aminobutyric acid.⁸ Furthermore, following the recent findings reshaping a stimulatory effect of the cholinergic system on GH secretion through the inhibition of the somatostatinergic tone, numerous studies have been directed to better clarify the role of this system on GH secretion.⁹ Furthermore, it is known that neuropeptides such as thyrotropin-releasing hormone (TRH), substance P and galanin contribute to modulate GH secretion via paracrine mechanisms.¹⁰ Moreover other hormones, such as leptin and ghrelin, have been recently proven to exert stimulatory effects on the release of GH.⁹ On the other hand the pituitary secretion of this hormone is pulsatile and follows a circadian rhythm with a peak concentration reached 1 hour after the onset of the sleep. GH expression levels

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are up regulated by metabolic factors such as low blood sugar, amino acids, exercise and stress, while they are down-regulated by hyperglycemia, and increased circulating FFA.^{10,11} Other hormones, such as glucocorticoids, thyroid hormones and gonadal hormones may act as GH regulators.^{12,13} Ultimately, the main effect of GH consists in stimulating mainly the hepatic synthesis and secretion of IGF-1, which mediates, in part, the metabolic effects of the pituitary hormone. The serum concentration of IGF-1, in turn exerts a negative feedback on the secretion of GH.^{14,15}

GH exerts a lipolytic effect mainly on the visceral adipose tissue and, to a lesser extent, on the subcutaneous adipose tissue. These effects result in an increase of the circulating levels of FFA.¹⁶ The effect of GH on adipose tissue consists in a reduction of glucose uptake and in an increased lipolysis. Unlike in adipose tissue, in the liver GH promotes the absorption of triglycerides by increasing the expression of lipoprotein lipase (LPL) and that of hepatic lipase.¹⁷ GH directly stimulates the uptake of amino acids into muscle cells, thus increasing protein synthesis and, consequently, muscle growth.¹⁷

GH plays a pivotal role in the regulation of the intermediary metabolism, body composition and energy expenditure (on the other hand, the hyperglycaemic, lipolytic and anabolic effects of this hormone are well known). Overall, GH acts by directing energy metabolism preferentially toward lipids oxidation, then towards glucose oxidation and finally to protein oxidation. This sequence of events ultimately provides the energy derived from the food needed for protein synthesis. GH also affects the body composition via its anabolic, lipolytic, sodium retaining effects and promotes bone mineralization. Among the different metabolic effects induced by GH, those exerted on lipid metabolism were the first to be recognized. The stimulation of lipolysis in adipose tissue leads to an increase of the circulating FFA. The presence of GH receptors on preadipocytes and adipocytes is of crucial importance for the lipolytic effect of GH mediated by LPL and by hormone-sensitive lipase (HSL), respectively. LPL is the enzyme responsible for the hydrolysis of the triglycerides contained in VLDL and chylomicrons and which is involved in the production of circulating in FFA which, in turn, are internalized and stored in the adipocytes. GH negatively regulates LPL by inhibiting the enzyme activity rather than the transcription of the gene encoding for GH. In this way GH decreases the adipose accumulation mainly at the abdominal compartment level. It is worth noting that the facilitating effects of GH on the proliferation and differentiation of preadipocytes may be also exerted through the paracrine/autocrine activity of Insulin Growth Factor-I (IGF-I) produced by the adipose tissue. Other enzyme involved in the regulation of adipogenesis such as HSL, promotes the normal lipolysis through the intracellular hydrolysis of triglycerides into glycerol and FFA. FFA are the energetic substrate needed for those tissues with a high metabolic rate, first of all skeletal muscle. The effects of GH on carbohydrate (CHO) metabolism are more complex. These effects may be indirectly regulated by antagonizing those induced by insulin. The final effect is the reduction in the metabolism of CHO to the detriment of lipids. The effects of GH on protein metabolism are also well known. Its anabolic activity on protein synthesis is the consequence of the stimulation of amino acid uptake by tissues and their incorporation in the proteins. The lipolytic and anabolic properties of GH may account for the role of this hormone in the regulation of body composition, its facilitating effects on the development of muscular component or its inhibiting effects on fat accumulation. Finally, the close relationship between nutrition and somatotrophic secretion is evident during the fasting and the postprandial period. In fact during fasting, and/or physical stress, GH

secretion is amplified, while the excess of nutrients, such as glucose and FFA, inhibits the release of GH.¹⁸⁻²⁶ Specific amino acids, in particular lysine and arginine (Arg), may also stimulate GH secretion.²⁷ This phenomenon is a clear proof about the correlation between GH and amino acid metabolism whose aim is to act as anabolic hormone (thus boosting protein synthesis), in presence of an excess of amino acids. However, GH plays a marginal role during the postprandial phase, while high levels of insulin inhibit protein catabolism and lipolysis. The significant relationship between GH and protein metabolism is confirmed by the fact that GH deficiency results in a net loss of lean body mass. These findings strongly support the hypothesis of close relationship between nutritional status and somatotrophic secretion.

Some nutritional factors function as regulators of the serum levels of Insulin-like growth factor-1 (IGF-1).²⁸ For instance, malnutrition and protein deficiency, are associated with a low level of this hormone. In man a fasting condition induces a marked decrease of IGF-1 circulating levels which after 10 days results in a 15-20% reduction as compared with baseline values. However, IGF-1 levels return to normal values following re-feeding.²⁹ These findings suggest that some nutritional factors may be involved in particular, in the modulation of IGF-1 secretion during malnutrition due to protein deficit nutrition.^{30,31} Several studies have shown that many protein foods are positively correlated with the IGF-1 levels, in particular: meat, fish, cheese, tofu, beans, lentils, yogurt, eggs, nuts, and seeds.^{32,33} In addition to protein foods, carbohydrate and lipids appear to have also a role in the modulation of IGF-1 secretion.³⁴

Until a few years ago, GH was thought to act mainly on children growth rather than to exert metabolic effects. However, growing evidence in these recent years has highlighted that GH plays a key role not only in puberty, but also in adulthood. For instance GH has been proven to be involved in a pathological condition which is well known as GH deficiency syndrome (GHD). This condition is characterized by metabolic, functional and structural changes such as increase of visceral fat, decrease of lean mass, osteopenia and/or osteoporosis, alterations in lipid and carbohydrate metabolism, decrease of muscle strength and exercise tolerance, increased mortality due to cardiac and cerebrovascular accidents, reduced psycho-physical wellness and therefore reduced quality of life rating.^{35,36} Short term studies have shown that the biological alterations associated with GHD may be reversible upon treatment with recombinant GH (rhGH).³⁷⁻⁴⁰ Current guidelines for the diagnosis of GHD in adults are primarily based on the indications of the GH Research Society (GHRS), which indicate that the diagnosis of GHD, must be demonstrated by the stimulation tests of GH secretion.⁴¹ The new recommendations, published in 2011,⁴¹ suggest to submit to the test for GHD to the following patients: i) Subjects with signs and symptoms of hypothalamic-pituitary disease of endocrine, structural and/or genetic origin; ii) Subjects who underwent cranial irradiation or clinical treatment for brain tumors; iii) Subjects with traumatic brain injury or subarachnoid hemorrhage.⁴¹

In order to diagnose GHD in adult patients, only one stimulation test is needed. The measurement of basal levels of IGF-1, as well as that of other markers, has not been considered appropriate to distinguish between subjects with normal GH levels and GHD subjects. Although normal levels of IGF-1 does not rule out a severe GHD, very low levels are highly suspicious for GHD. Therefore, it is currently suggested that in the absence of other catabolic conditions, and/or liver disease, very low levels of IGF-1 may be considered diagnostic for the presence of severe GHD. Moreover, the deficiency of three additional pituitary hormones is

considered highly predictive for GHD.⁴² However, the insulin tolerance test (ITT) is considered the *gold standard* for diagnosis of GHD. The degree of severity of GHD is defined in presence of GH levels $< 3 \mu\text{g/L}$. On the other hand, Aimaretti *et al.*⁴³ have shown that GH values comprised between 3 and 5 $\mu\text{g/L}$ following stimulation with ITT represent the first and the third centile of the results of the test in lean subjects. However, this test is contraindicated in certain types of patients, such as those showing evidence of electrocardiographic abnormalities or with ischemic heart disease, epilepsy or brain damage, or in elderly patients.⁴⁴ In patients where the ITT test is contraindicated, other stimulation tests should be used. To date, the GHRH + Arg test is the most widely used in patients with suspected GHD of pituitary origin. This type of test is usually well tolerated and does not cause serious side effects such as ITT induced hypoglycaemia. If the values of Body Mass Index (BMI) are taken as cut-off limit, then severe GHD is defined in presence of GH levels $< 11.5 \mu\text{g/L}$ in lean subjects ($\text{BMI} < 25 \text{ kg/m}^2$); $< 8 \mu\text{g/L}$ in overweight subjects ($\text{BMI} 25 - 30 \text{ kg/m}^2$) and $< 4.2 \mu\text{g/L}$ in obese subjects ($\text{BMI} > 30 \text{ kg/m}^2$).⁴⁵ The response to GHRH + Arg negatively correlates with age, and BMI.⁴⁶⁻⁴⁸

The goal of the replacement therapy with GH is the correction of structural functional and metabolic abnormalities which are a characteristic of GHD. According to the GHRH guidelines the starting daily dose of GH to be administered should be 0.2-0.3mg/day in man and woman respectively, and 0.1 mg/day in older patients independent of patient body weight.⁴⁹ In fact, this parameter is not recommended for adjusting the dose as this molecule undergoes wide inter-individual variation of absorption and response. Another reason is that the administration of increased level of doses in patients with higher weight is not in use. Recently it has been shown that the response to GH treatment may vary according to the gender.⁵⁰ In fact men appear to be more responsive than women to GH treatment. This phenomenon results in an improving of body composition, lipid metabolism and bone mass.⁵⁰ In order to monitor appropriately the clinical response to GH, a baseline assessment of body composition, bone mineral density, lipid and glucose metabolism and psychophysical conditions are required.⁵¹

Body composition in adults with growth hormone deficiency syndrome

Adult patients with GH deficiency syndrome (GHD) show modifications of body composition.^{35,36} These patients have an increased fat mass (FM), with a characteristic distribution of fat in the abdomen, and a reduction of lean body mass (FFM).^{37,38} In addition, these patients show a reduction in total body water as compared to normal subjects.³⁷⁻⁴⁰ These alterations are present to a greater extent in patients whose hormone deficiency occurred during childhood than in patients whose deficiency occurred in adulthood.⁵² Furthermore, it has been reported that alterations in body composition are related to the severity of the GHD.⁵³ Numerous studies have shown mainly a significant reduction of visceral FM and, to a lesser extent an increase of FFM in response to therapy with rhGH.⁵⁴⁻⁵⁶ Likewise as observed for muscle mass, several studies have shown after treatment with rhGH an increase in isometric strength and isokinetic contraction, accompanied by an increase physical exercise performed.^{57,58}

GH has been shown to stimulate not only the longitudinal bone growth during childhood and adolescence but also regulates bone turnover throughout the lifetime.⁵⁹ Clinical evidence shows that adult patients with GHD have a significant reduction in bone

mineral density, which mainly involves the trabecular bone and are at high risk of osteoporotic fractures of vertebral column.⁶⁰ According to recent studies, the replacement therapy with rhGH induces important effects on bone metabolism.⁶⁰ However these effects appears to be less marked in patients with adulthood GH than in patients with pediatric GH deficiency.⁵⁵ This difference may be likely due to the attainment of a normal peak bone mass in patients who acquire the deficit in the elderly.⁶¹

Numerous epidemiological studies have demonstrated that adult hypopituitary patients with GHD undergoing replacement therapy for deficits of all pituitary hormones but not for GHD, had a shortened life expectancy and a twofold increased risk of cardiovascular and cerebrovascular diseases as compared to controls.⁶² Although many other factors may contribute to increase this risk, it was suggested that GHD might play a predominant role. In addition to the structural and functional alterations of cardiac muscle, the increased mortality from cardiovascular events in patients with GHD appears to be the result of changes in body composition, lipid metabolism, blood pressure, insulin resistance and presence of chronic inflammatory conditions.^{62,63}

Adult patients with untreated GHD show a significant reduction in quality of life (*QoL*) in terms of reduction of vitality, tendency to social solitude and emotional alterations. These conditions may improve following a replacement therapy with GH. The positive effects of this therapy are due to an improvement in cognitive functions such as memory and concentration, mood, psychological well-being and physical strength. In particular, patients with juvenile-onset GHD *QoL* appear to be less influenced.⁵¹

Thyroid hormones nutrition and obesity

The pulsatile secretion and the circadian rhythms of thyroid hormones are stimulated by thyrotropin (TSH) produced by thyrotrophic cells of the anterior pituitary. TSH secretion, in turn, is stimulated by TRH.⁶⁴ The secretion of TSH is also inhibited by very small increases of thyroid hormones concentrations and in response to small decreases of triiodothyronine (T_3) and thyroxine (T_4). The physiological role of TRH is that to regulate thyroid hormone induced TSH secretion. Other mechanisms that mediate this effect are a decrease in the TRH secretion from the hypothalamus and a decrease of the number of TRH receptors on pituitary cells respectively. Furthermore, TRH activity can be inhibited by somatostatin, dopamine and elevated concentrations of glucocorticoids.⁶⁴ In conclusion, the thyroid axis represents a classic example of *feedback loop of endocrine system*: hypothalamic TRH stimulates the pituitary TSH production which, in turn, stimulates the synthesis and secretion of thyroid hormone. Thyroid hormones, inhibit the production of TRH and TSH by a negative feedback mechanism.⁶⁵ The homeostatic *set point* of hypothalamus pituitary thyroid (HPT) Axis is determined by TSH.

Deiodinase (5'-iodothyronine deiodinase), is an enzymes that convert T_4 to T_3 . Deiodination is the main metabolic pathway of thyroid hormone.⁶⁶ The daily production of T_3 account for the 20% of its total production, while the remaining 80% results from deiodination in peripheral tissues. The process of deiodination is mediated by a series of three types of enzymes *i.e.*, the iodothyronine deiodinase (ID).⁶⁷

Deiodinase I (ID-I), is important for the production of T_3 from T_4 in peripheral tissues. The enzyme is present in the kidney, in the endoplasmic reticulum of the liver cells and in the plasma membrane of renal and thyroid cells.⁶⁸ Deiodinase II (ID-II).

This enzyme is present in the brain, pituitary, brown adipose tissue and placenta. In humans, ID-II is also expressed in the thyroid gland, heart, and skeletal muscle. ID-II is endowed with deiodinase activity located in the outer ring. Therefore it is important for the intracellular production of T₃ in these tissues. It also keeps constant T₃ levels in the central nervous system.⁶⁸ Deiodinase III (ID-III) is present in the brain, skin, placenta and in some foetal tissues. It is endowed with deiodinase activity located only the inner ring and therefore allows the production of reverse T₃ (rT₃), an inactive form of T₃, from T₄.⁶⁹

An increasing number of studies in these recent years has been carried out in order to investigate the possible relationship between body weight and thyroid function. It is well known that hyperthyroidism leads to weight loss while hypothyroidism is associated with weight gain and a generalized distribution of adipose tissue. However, the changes of the thyroid function in obesity are still controversial. In fact, obesity, and in particular the android phenotype, is associated with multiple endocrine abnormalities such as insulin resistance, gonadal dysfunction, alterations of both pituitary adrenal and somatotrophic axis.⁷⁰ On the other hand, the relationship between obesity and thyroid dysfunction are still not well understood.⁷¹ Obese subjects present alterations of the thyroid functions, in particular, an increase of TSH (in the absence of thyroepathies), and that of T₃, *i.e.*, the metabolically active form of the hormone.^{72,73} Conversely, no changes are observed in total and free T₄, whose levels are similar in obese and normal weight. In addition, fasting and overeating do not influence the concentrations of serum T₄. This phenomenon demonstrates the lack of relationship between circulating T₄ and body weight.⁷⁴ Alterations in the negative feedback of HPT axis, occur in obese subject. These effects result in an increase of T₃ that is not followed by a reduction of TSH. It is well known that in obese subjects TSH and body mass index (BMI) are positively correlated.⁷⁵ In fact, many studies undertaken in children, adolescents, and adults have shown that TSH levels increased slightly in the obese subjects, compared to normal weight subjects. In a cross-sectional study, Knudsen *et al.*,⁷⁶ showed that, in addition to the positive correlation between BMI and serum TSH, an increase in BMI is associated with an increase in serum TSH levels within 5 years. These data were confirmed by another longitudinal study of Svare *et al.*⁷⁷ High levels of TSH in obesity may be due to a neuroendocrine dysfunction that causes an abnormal secretion. In particular leptin, a hormone produced by adipocytes, has been shown to alter the HPA axis.⁷⁸ In humans, leptin and TSH undergo a very similar circadian rhythm. Leptin deficiency is closely associated with the deregulation of pulsatile patterns and circadian rhythm of TSH secretion.⁷⁹ These findings suggest a possible role of leptin in the regulation of TSH with resetting the thyroid axis.^{80,81} On the other hand the production of TSH is also regulated by neurotransmitters and hormones repletion as neuropeptide Y, α -melanocyte-stimulating hormone, and agouti-related peptide (AgRP) that regulate body weight and activate the hypophysiotropic thyrotropin-releasing hormone (TRH) neurons. These transmitters are influenced by leptin, which at peripheral level, modulates, also mono-deiodinase in different tissues, depending on the energy status. These results suggest that TSH levels may be considered as marker of alteration of the energy balance in obesity. In addition, the increased TSH levels may indicate the presence of a hormone-resistance status. Despite the increased levels of TSH, T₃ remains elevated too. This effect seems to be due to a decreased expression of TSH receptors in peripheral tissues which, in turn, leads to a *down-regulation* of thyroid hormone receptors and consequently to an increase of TSH and free T₃ (fT₃) levels.^{82,83} Total and free T₄ (fT₄) levels do not undergo

evident changes in obese subject, while a moderate increase in TSH is associated with a slight increase in fT₃, total T₃ and thyroid volume respectively.⁸⁴ The slight increase of fT₃ levels in obese subjects could be interpreted as compensation mechanism following to an excessive accumulation of fat mass and an increased type II deiodinase activity that converts T₄ to T₃, in order to increase the energetic expenditure.⁸⁵ In this context, a positive association between fT₃/fT₄ ratio (*i.e.*, the deiodination index), waist circumference and BMI,⁸⁶ has been highlighted in obese patients. These data suggest that, due to the increased deiodinase activity, a high rate of conversion from T₄ to T₃ may occur, as a compensatory mechanism to the increase of adipose tissue. These effects lead to an increase in the rate of basal metabolism and, consequently, to an improvement in energy expenditure. Ultimately, TSH and fT₃ levels are elevated in obese patients. Assuming that the inappropriate increase of TSH is caused by a reduced inhibitory effect of leptin, then the increase of fT₃ should be considered an adaptative mechanism to the changes in mono-deiodination, that decrease to the rate of energetic source available for conversion into fat.⁸⁷ In line with this hypothesis, the high levels of TSH in obese subjects tend to normal value following a substantial weight loss. In addition, thyroxine based therapy in obese patients with moderately elevated levels of TSH does not affect body weight or lipid profile. Clinical observations have highlighted that in the obese patients on diet, the treatment with T₃ and T₄, even at physiological doses, induces a subclinical hyperthyroidism. Therefore, this therapy should be discouraged in obese, euthyroid patients. These findings question the diagnosis of subclinical hypothyroidism in obesity and indicate that a slight increase in TSH levels is a consequence rather than a cause of obesity. Furthermore, as mentioned previously, thyroid hormones, in particular triiodothyronine or T₃, should be used in the long term treatments of obesity due their ability to increase energy expenditure. However, due to the onset of thyrotoxic side effects, *i.e.*, increased heart rate, cardiac hypertrophy, decreased lean body mass, alteration of hypothalamus-pituitary-thyroid axis, the clinical use of T₃ as an anti-obesity drug has been abolished. Recently, it has been shown that the 3,5-diiodo-L-thyronine (T₂), a naturally occurring iodothyronine produced by the thyroid, is endowed with biological activities similar to those of T₃ but is devoid of tireotoxic effects.⁸⁸ Recent experimental *in vivo* studies have shown that the administration of T₂ in rats fed diets rich in lipids induces a decrease of circulating cholesterol and triglycerides and a reduction of body weight without inducing hepatic steatosis.⁸⁹ These data demonstrate that multiple treatments with high doses of T₂ inhibits the secretion of TSH and prevents the onset of hepatic steatosis in rats fed diets rich in lipids.⁸⁹

Increasing evidence indicates the presence of possible interactions between nutrition and endocrine system. Food exerts marked short term and the long term effects on the production of hormones and their blood levels. At the same time, many physiological effects of foods are regulated by hormones.⁹⁰ Thyroid function also is susceptible to acute and chronic alterations induced by quality and quantity of ingested nutrients. Thyroid hormones exert important functions aimed at maintaining energy homeostasis. In fact thyroid gland plays a central role in the regulation of energy metabolism, thermogenesis, glucose and lipid metabolism. Additionally, thyroid gland is also involved in the regulation of food intake.⁹¹ The effects of thyroid hormones on glucose metabolism influence several biological functions. In fact fT₃ increases the rate of gastrointestinal absorption of carbohydrate, and modulate glycolysis, gluconeogenesis and insulin secretion.⁹¹

On the other hand, carbohydrate play an important role on the metabolism of thyroid hormones.⁹²

In this context although T_4 represent the main hormone secreted by thyroid gland, it is only a *pro-hormone* that need to be converted to T_3 in the peripheral tissues, through a deiodination reaction involving the outer rings of T_4 .⁹³ Numerous studies have shown that carbohydrate are able to significantly modulate the reactions of deiodination of T_4 to T_3 . For instance, in humans, serum T_3 levels are directly correlated to the rate of CHO intake.⁹⁴ This results in an increase of the thyroxine 5'-monodesiodase activity in the brown adipose tissue and in the liver. However no significant changes in serum levels of thyroid hormones occur.⁹⁵ Several studies have also revealed that, in humans the rate of synthesis of T_3 from T_4 that decreases during fasting and returns to normal levels during re-feeding.⁹⁶ In particular, the re-feeding with CHO, is able to revert the changes occurred in serum levels of T_4 , T_3 , rT_3 .⁹⁷ Finally thyroid hormones have many effects on the regulation of lipids synthesis, absorption and metabolism.⁹⁸ These molecules act on 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is the key enzyme in the biosynthetic pathway of cholesterol.⁹⁸ In addition, several studies have shown that serum lipids are associated with TSH levels.^{99,100} On the other hand, the increased consumption of dietary fats in Western-type diets, which is one of the main factors responsible for the increase in body weight, has been correlated with specific alterations of thyroid axis functions.¹⁰¹ Furthermore, it has been observed that the dietary intake of oxidized lipids may induce an increase in the plasma levels of total T_4 , in part by interfering with the circulating levels of selenium, a component of the deiodinase type I enzyme whose role in the metabolism of thyroid hormones is well known.¹⁰² Finally, it is well established that TSH levels are correlated with circulating lipids.¹⁰³ Early evidence have indicated that oxidized fats may increase T_4 levels.¹⁰⁴

Diet, obesity and hormones

Several studies have shown that the adoption of a Mediterranean diet (MD), provides protective effects against most of the widespread chronic diseases.¹⁰⁵ In these studies, the concept of MD has been translated into a diet characterized by: i) a high consumption of vegetables, legumes, fruits and nuts, olive oil and cereals (which in the past were mainly wholemeal); ii) a moderate consumption of fish and dairy products (especially cheese and yogurt) and red wine during meals; iii) by a low consumption of red meat, white meat and saturated fatty acids.¹⁰⁶ In line with these observation studies of Esposito *et al.*¹⁰⁷ have reported that in adults the strict adherence to MD resulted in the prevention of hypertension, hypercholesterolemia, diabetes and obesity. On the other hand meta-analysis studies conducted by Sofi *et al.*¹⁰⁸ have shown how MD act as a protective factor against all causes of mortality, in particular those related to cardiovascular disease or cancer, and also to Parkinson's disease and Alzheimer's disease. In a recent study carried out on Spanish and Italian subjects, Baldini showed how the younger generations seem to gradually and steadily leave MD, in favor of new food trends which are characterized mainly by foods high in fat.¹⁰⁹ The benefits of MD on healthy status are well documented.¹¹⁰ There is convincing evidence that the adherence to the traditional MD was associated with an increase in lifespan,¹¹¹ a reduction in global mortality, lower incidence of coronary heart disease and atherosclerosis, metabolic syndrome (MetS) and the biochemical markers of Insuline resistance (IR), inflammation or risk of cardiovascular diseases.¹¹² However, few prospective studies have investigated the association between adherence to the

MD and risk of obesity.^{113,114} There are several physiological effects that may explain why the key components of MD may protect subjects from increase of body weight thus preventing the onset of obesity. MD is rich in plant-based foods that provide a large amount of dietary fibres which increases satiety and increases the secretion of Cholecystokinin.¹¹⁵ The MD foods have a low energy density, a low glycemic index and a high water content. These characteristics provide a full satiety and a lower calories intake, thus fostering the prevention of weight gain. MD contains high levels of mono-unsaturated fat, which provide about 67% of energy from fat, and low levels of saturated and trans-unsaturated fats. This pattern of fatty acids expression may provide important benefits on the health status.^{116,117} In fact, diets rich in monounsaturated fat, appear to improve glucose metabolism, and increase post-prandial fat oxidation as compared to diets rich in saturated fats. These phenomena may provide, in part, an explanation on why the consumption of olive oil is less likely to cause an increase of body weight.

The history of milk is as old as the history of the mankind itself. Since several millennia milk has been one of the staple of foodstuffs. Different types of milk such as sheep, goat, donkey in addition to breast milk can be used for human consumption in the first period of life. However, in general when talking about milk, this term refers to cow's milk. Milk is composed for 87% of water in which are dispersed protein of high biological value (3.3%), fats, (mainly saturated short-chain fats) (3.6%), easily digestible, sugars (4.9%) mainly lactose, a disaccharide sugar composed of galactose and glucose. Vitamins which are present in large amounts in milk are, among the liposoluble vitamins, vitamin A and carotenes, and vitamin B1, B2, vit. B12 and pantothenic acid among the water-soluble vitamins. Among milk minerals, of particular importance for human nutrition is calcium, whose milk is the main source (120 mg/100g), and which is present in a form that is easily absorbed by the body.¹¹⁸ Recent growing clinical evidence, suggests that the increased amount of calcium in the diet is associated with a preventive effect of some risk factor related to cardiovascular diseases such as hypertension, overweight, obesity, and metabolic syndrome.¹¹⁹⁻¹²¹ The NHANES study McCarron *et al.* carried out in the early 1980s on 10,000 subjects aged 18-74 years, highlighted an inverse association between high intake of calcium in the diet and body weight.¹²² These observations were confirmed by subsequent NHANES III studies of Zemel *et al.*¹²³

These two studies have laid the groundwork to investigate the correlation between calcium intake (and milk) and body composition in humans. To date, numerous observational studies, mainly cross-sectional studies and retrospective studies have examined the relationship between rate of milk intake and body weight variation.^{124,125} Most of these studies have highlighted a statistically significant inverse association between these two parameters thus suggesting that low levels of milk intake is associated, either in children or in adults, with an increase of fat mass and an increased risk of developing overweight and obesity over the time. However, a few randomized controlled clinical investigations have examined the effect of a higher intake of milk on body weight. Other studies have shown an inverse association between dietary calcium levels in particular from dairy sources, and body weight in children and in adults. In particular, a study carried out by Barba *et al.*¹²⁶ showed that milk consumption was significantly inversely associated with BMI (Z-score). This was the first study reporting a significant inverse association between rate of milk consumption and BMI in children. In 2006 a cross-sectional study by Marques-Vidal *et al.*¹²⁷ evaluated the relationship between milk consumption and body mass index in a Portuguese adult population.

These investigations showed a significant negative correlation between higher consumption of milk and BMI. Finally, a randomized controlled clinical trial of Gilbert *et al.*¹²⁸ carried out to assess the influence of milk supplementation on appetite markers in obese women undergoing weight loss concluded that milk supplementation attenuates the orexigenic effect, thus leading to more consistent weight loss.

There are currently several physiological mechanisms proposed to explain the anti-obesity effect of milk.¹²⁸

There is evidence that in adipocytes, the intracellular calcium ($[Ca^{2+}]_i$) decrease the rate of lipogenesis.¹²⁹ The intake of dietary calcium is inversely associated with ($[Ca^{2+}]_i$) levels. This phenomenon which has been observed to occur *in vitro* (on adipocyte cultures) and *in vivo* (in mice) is well known as the *calcium paradox*.¹²⁹ The studies show that the amount of Ca^{2+} intake from the diet is inversely associated with the levels of ($[Ca^{2+}]_i$). Therefore, an increased calcium intake leads to a reduction of ($[Ca^{2+}]_i$), to an increased lipolysis and to a body weight loss. This paradoxical effect is explained by the equilibrium established between dietary calcium intake and calcium-regulating hormones dependent on $[Ca^{2+}]_i$.¹³⁰

Human studies have confirmed that calcium supplementation in the diet results in significant suppression of intact parathyroid hormone (iPTH) and calcitriol. These effects lead to a reduction of $[Ca^{2+}]_i$ resulting in increased lipolysis and body weight loss.¹³¹

Besides the *calcium paradox*, the anti-obesity effect of milk had been explained by the increase in fecal excretion of fats caused by calcium.¹³² The mechanisms by which calcium may increase fat excretion is probably the result of an interaction between calcium itself and saturated fatty acids, which cause the formation of insoluble fatty acid soaps thus leading to a lower fat absorption.¹³² The excretion of fecal fat induced by calcium has also been demonstrated to occur in humans. In fact several intervention studies, have shown that an increased dietary calcium intake induced steatorrhea.^{133,134} Other mechanisms have been proposed to explain the thwarting effects of milk on obesity and in particular: i) Calcium may cause a reduction in the cortisol production in adipocytes by inhibiting the expression of 11β -hydroxysteroid dehydrogenase, the enzyme that converts cortisone to cortisol, thus leading to a lower visceral fat accumulation;¹³⁵ ii) Increased expression of Mitochondrial uncoupling proteins 2 in white adipose tissue and consequently thermogenesis;¹³⁶ iii) Nicotinamide riboside, a precursor of vitamin B3, present in milk, appears to play an important role in preventing obesity. It acts by improving antioxidant activities;¹³⁷ iv) It has been reported that milk proteins can suppress the recruitment of short-term food, by regulating the hunger and satiety mechanisms.¹³⁸

Several investigations have been directed to assess the influence of nutrition on the endocrine axis in obese subjects. The study evaluated the influence of nutrition on the endocrine axes by following two lines of investigational approaches: the first was based on the assessment of body composition in relation to the functional dysregulation of somatotropin axis while, the second one was focused on the influence of nutrition on the endocrine axes and the adherence to the MD.¹³⁹ With regard to the first research line, endocrine changes associated with obesity and its phenotypic variability were evaluated in a cohort of subjects with moderate to severe obesity who were eligible for bariatric surgery. In line with previous observations from other studies GH deficiency has been found in almost half of the subjects.¹³⁹ As expected, GHD subjects showed a higher prevalence of hypercholesterolemia and type 2 diabetes. Additionally these subjects also showed statistically significant differences in anthropometric and metabolic parameters. In addition, GHD subjects showed to have greater FM and FFM

less than normal GH levels subjects. Instead, more than half of the subjects showed deficient levels of IGF-1, which were associated with a higher prevalence of hypercholesterolemia and MetS when peripheral mediators of GH effects were considered. In particular, individuals with deficits of IGF-1 showed no statistically significant differences in anthropometric, metabolic and hormonal parameters when compared to the group with sufficient levels of IGF-1 while, they showed a higher FM and a lower FFM. The association between low levels of IGF-1 and MetS was also confirmed by recent studies.^{140,141} Among the main anthropometric parameters considered, as a surrogate of central adiposity, circumference vitae, resulted the best predictor of GH secretion, which was not related to BMI. In agreement with other previous studies, this effect emphasizes the role of visceral fat in influencing the decrease of GH secretion.¹³⁹ In particular, it has been shown that 1cm increase in circumference vitae is associated with a decrease of GH peak of about $1\mu\text{g/L}$.¹⁴² Thus, in line with previous studies, the results of the first line of research showed that the increased visceral adiposity contributes to the reduction of GH secretion. The deficiency of the secretory GH/IGF-1 axis due to the increase of visceral fat, can contribute in turn to determine a further accumulation of visceral fat, thus creating a sort of maladaptive circuit, which may result in an increased risk of cardiovascular diseases. These findings also shows that the assessment of body composition in obese, in terms of anthropometry and bioimpedentiometry, could be a useful initial screening to identify those subjects at higher risk of deficiency of GH secretion and for which the GHRH + Arg test could, likely, have a positive result.

The second line of research, was directed at evaluated the adherence to the MD and the influence of nutrition on the endocrine axes in subjects with moderate and severe obesity eligible for bariatric surgery in this case too.

By dividing the population into males and females, the percentiles for BMI, circumference vitae and age were calculated, from which it was observed that the subjects with the greatest adherence to the MD are those in the lowest percentile of BMI and circumference vitae, both for males and females, with circumference vitae as a major predictor of adherence to linear regression MD. In particular, it has been highlight that the free leptin index (FLI) positively correlated with foods typical of the MD (*i.e.*, extra virgin olive oil, vegetables, legumes, fish, poultry and nuts) and the total caloric content, whereas no correlation was observed with the nutrients distribution. The MD is an example of diet endowed with anti-inflammatory and anti-oxidant effects.¹⁰⁶ These effects could, in part, explain the correlation with the FLI. There are few epidemiological studies that have investigated the potential impact of a complete dietary pattern (namely, the diet, not individual foods), on the characteristics of non-alcoholic fatty liver disease (NAFLD) and its severity. Recently, a clinical intervention study of Ryan *et al.*¹⁴³ showed that the MD improves insulin sensitivity and NAFLD as compared with a low fat content and high carbohydrate content.¹⁴³ Although a greater adherence to the MD was not associated with a lower risk to develop NAFLD, the subjects with a strict adherence to this model appear to have a beneficial effect on the severity of the disease as assessed by the FLI. These results suggest that diet, especially the Mediterranean model, it is an important factor in the pathogenesis and development of NAFLD. The results indicate that the composition of the diet may influences the severity and progression of the disease by increasing the inflammation and oxidative stress. On the other hand, in our study, nut consumption appears to be the best predictor for FLI.¹⁴³

Several studies have investigated the correlation between nuts consumption and cardiovascular diseases.¹⁴⁴ However few

investigations have investigated the correlations between consumption of nuts and NAFLD.¹⁴⁴ In terms of energy and nutrients, 30 g of dried nuts provide 206.6 Kcal, distributed as 4.3g of protein, 20.4g of fat, 1.5 g of carbohydrate, and 1.9 g of fibers.¹⁴⁵ Due to their content of α -tocopherol and selenium, as well as vitamins of the B group, such as B1 and B6 and minerals such as copper, zinc, phosphorus and magnesium, nuts are considered an important source of antioxidants.¹⁴⁶ The anti-oxidant effects of nuts, appears to be the consequence of a particular composition in polyunsaturated fatty acids, such as linoleic acid (30.02%), α -linolenic acid (6.64%) and monounsaturated, such as oleic acid (9.38%), as well as from the content in plant sterols, polyphenols, minerals (particularly magnesium and potassium).¹⁴⁷⁻¹⁴⁹ Furthermore, Tapsell *et al.* have shown that the intake of 30 grams of nuts /day (about 5-6 nuts) leads to an improvement of the lipid profile.¹⁵⁰

In a subgroup of 50 patients with moderate to severe obesity underwent hospitalization due to thyroid dysfunction it was observed that, in obese subjects TSH levels were positively correlated with BMI and waist circumference. Furthermore, these results were also confirmed by bioelectrical impedance analysis, which showed a positive correlation between TSH and FM. Finally positive correlations were also reported between TSH, blood glucose, insulin and HOMA-IR index. From a strictly dietary and nutritional point of view, the results of this study also showed that the deiodination index, expressed by the fT_3/fT_4 ratio, was positively correlated with the percentage of CHO and negatively correlated with the percentage of fat present in the diet but not with the total caloric value. CHO content was proven to be the best predictor of fT_3/fT_4 ratio by linear regression analysis. The positive association between TSH, BMI and waist circumference is commonly reported among obese subjects.^{74,75} The correlation between TSH and BMI may be mediated by leptin, an important regulator of neuroendocrine HPT axis.⁸⁰ This effect may be considered as the consequence of the positive influence of TSH on adipogenesis which results in an increased release of insulin to compensate for IR.⁸⁰ Other studies analyzed the onset of resistance to insulin receptors that may be associated with a resistance of thyroid receptors.⁸³ However it is unclear whether the positive correlation between IR and TSH levels should be interpreted as a consequence of metabolic resistance of receptors for thyroid hormones or as the positive effect of the influence of TSH on adipogenesis as a consequence of the increased release of insulin to counteract IR. Although it is known that the deiodination is strongly influenced by nutritional metabolic factors, few experimental observations, (none of which obtained from human studies), have documented a possible influence of qualitative and quantitative differences of nutrients intake on the relationship between thyroid function and obesity.^{151,152} Numerous studies have demonstrated that CHO are able to modulate the peripheral metabolism of thyroid hormones by deiodination of T_4 to T_3 in the liver via the enzyme 5' deiodinase type 1.^{93,94} In humans, T_3 serum levels are directly associated with rate of CHO intake.¹⁵³ In particular, during caloric restriction diet, especially diets low in CHO, the reduction of the production peripheral T_3 induces a decrease reduction of fT_3 blood levels.¹⁵⁰ Several studies have also revealed that in humans, the production of T_3 from T_4 decreases during fasting and is restored following re-feeding.^{94,96} In particular, the re-feeding, with CHO, is able to reverse the changes in serum T_4 , T_3 , rT_3 and TSH caused by fasting.⁹⁷ Instead, meals rich in CHO induce a significant increase in the 5'-deiodinase activity both in brown adipose tissue and the liver which are not associated with significant changes in serum levels of thyroid hormones.^{153,154} However, in the case of high-calorie diet, especially diet rich in carbohydrates, T_3 levels increase,

those of rT_3 decrease, while the levels of the T_4 do not undergo substantial changes.¹⁵⁵ Regarding lipids, previous studies have shown their effects on thyroid function.¹⁰² In particular, in vivo experiments showed that the increase in the content of oxidized lipids resulted in an increase in circulating levels of T_4 . This effects may be probably due to a reduction of the circulating levels of selenium and a consequent reduction in the activity of the type I 5'desiodase.¹⁰⁴

Conclusions

The complications regarding the neuroendocrine axes arising in overweight patients as a consequence of obesity, are not well known. Although secondary, the dysregulation of the endocrine system, may act by amplifying the metabolic alterations and body composition. These changes contribute to the variability of phenotypic expression in obese subjects and worsen the cardio-metabolic and cancer risk.^{156,157} Increasing evidence highlights a close relationship between nutrition and endocrine system. Data from other studies are in agreement with the reduction of GH secretion in obese subject and the secretory deficit of the GH/IGF-1 which take place in a functional manner following the increase of visceral fat. These effects may, in turn, contribute to determine a further accumulation of visceral fat thus increasing the risk of cardiovascular and metabolic diseases. As far as it concerns thyroid hormones, the peripheral deiodination, assessed by the fT_3/fT_4 ratio, is positively influenced by CHO content and negatively by the lipid content of the diet, but not by the total caloric value.⁹⁴ The effects of nutrients on thyroid hormone metabolism suggest that it is necessary to take into account the nutritional asset of patients. Therefore, the nutritional analysis associated with thyroid function may be important and may help to find the appropriate therapeutic approach which may be helpful to personalize dietary regimes. In fact foods, may exerts powerful, immediate and long term effects on the production of circulating hormones and, at the same time, many physiological actions of the foods take place by hormonal intervention. Therefore, the results underline the importance of an appropriate evaluation of body composition and nutritional profile, not only in terms of caloric intake, but also in terms of nutrients distribution as an essential prerequisite in the assessment of endocrine axes in obese subjects.

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