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Title: ***Lifestyle, metabolic disorders and male hypogonadism – A one-way ticket?***

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Abbreviation list:

BPA – Bisphenol A; BW – Body Weight; DMR – DNA methylation region; DDT – dichloro-diphenyl-trichloroethane; E_2 – Estradiol; EMAS – The European Male Aging Study; FSH – Follicle Stimulating Hormone; GnRH – Gonadotrophin Releasing Hormone; HH – Hypogonadotropic Hypogonadism; HPG – hypothalamus-pituitary-gonad; KlS – Klinefelter Syndrome; LC – Leyding Cell; LH – Luteinizing Hormone; MetS – Metabolic Syndrome; RCT – Randomized Clinical Trial; SC – Sertoli Cell; SMSNA – Sexual Medicine Society of North America; T – Testosterone; T2D – type 2 diabetes; TRT – Testosterone Replacement Therapy.

ABSTRACT

Hypogonadism is more frequent among men with common metabolic diseases, notably obesity and type 2 diabetes. Indeed, endocrine disruption caused by metabolic diseases can trigger the onset of hypogonadism, although the underlying molecular mechanisms are not entirely understood. Metabolic diseases are closely related to unhealthy lifestyle choices, such as dietary habits and sedentarism. Therefore, hypogonadism is part of a pathological triad gathering unhealthy lifestyle, metabolic disease and genetic background. Additionally, hypogonadism harbors the potential to aggravate underlying metabolic disorders, further sustaining the mechanisms leading to disease. To what extent does lifestyle intervention in men suffering from these metabolic disorders can prevent, improve or reverse hypogonadism, is still controversial. Moreover, recent evidence suggests that the metabolic status of the father is related to the risk of inter and transgenerational inheritance of hypogonadism. In this review, we will address the proposed mechanisms of disease, as well as currently available interventions for hypogonadism.

Keywords (5 words)

Hypogonadism, metabolic disorder, lifestyle, lifestyle intervention, transgenerational effects.

1. Introduction

Hypogonadism in adult men is a condition characterized by diminished levels of testosterone (T) (Basaria, 2014, Lunenfeld et al., 2015). According to this broad definition, hypogonadism can result is several effects in other organs and systems, as well as in general wellbeing. Therefore, according to the guidelines recommended by the Endocrine Society, hypogonadism should only be diagnosed “in men with symptoms and signs consistent with T deficiency and unequivocally and consistently low serum T concentrations” (Bhasin et al., 2018). Hypogonadism is classically classified according to its origin, as primary or secondary hypogonadism (Table 1). Primary hypogonadism (or hypergonadotropic hypogonadism) results from testicular failure to produce T (Ahern et al., 2016, Ventimiglia et al., 2017). Secondary hypogonadism (or hypogonadotropic hypogonadism) results from hypothalamic-pituitary endocrine dysfunction (Fraietta et al., 2013).

Hypogonadism can be further divided into organic or functional, according to its etiology (Table 1) (Bhasin et al., 2018). Organic etiologies are usually irreversible and on-site, such as inborn defects of metabolism or anatomical and morphological damage to the hypothalamus-pituitary-gonadal (HPG) axis (*e.g.* cancer, radiation, trauma) (De Roux et al., 2003, Khera et al., 2016). Functional etiologies are virtually reversible and related to other systemic diseases such as metabolic disease (obesity and type 2 diabetes (T2D)), lifestyle and environmental contaminants (Bhasin et al., 2018, Fraietta et al., 2013).

The worldwide prevalence of hypogonadism associated with organic etiologies has not suffered major fluctuations over time. However, the prevalence of functional hypogonadism has been increasing in parallel with the prevalence of

common metabolic disorders related to lifestyle, namely eating habits and sedentarism. Therefore, hypogonadism has also been linked to metabolic disorders, as both conditions are intimately correlated to hormonal alterations, including the disruption of the HPG axis, with consequent impairments of T secretion, spermatogenesis and sperm parameters (Alves et al., 2013, Oliveira et al., 2017, Samavat et al., 2018, Strain et al., 1982, Tajar et al., 2010). This evidence led to the recognition of another type of hypogonadism, which combined characteristics of both primary and secondary hypogonadism (Table 1). This disorder, characterized by both lower T and gonadotropin secretion, associated with chronic metabolic diseases and adult-onset, was coined as Late-onset Hypogonadism (LOH) (Morales and Lunenfeld, 2002, Wang et al., 2009) or Adult-onset Hypogonadism (AOH) (Khera et al., 2016).

Environmental and lifestyle variables can also influence the incidence of hypogonadism related to inborn errors (Khera et al., 2016, Stuppia, 2019), and have also been involved in the early-onset of metabolic and male reproductive dysfunction later in life (Crisóstomo et al., 2019, Manikkam et al., 2013). Emerging data elicits the inter and transgenerational epigenetic inheritance of signatures induced by lifestyle factors, on the onset of hypogonadism (Butler, 2011, Manikkam et al., 2013, Skinner, 2008). Summarily, hypogonadism may result from a pathological triad that includes an unhealthy lifestyle, the onset of metabolic disorder and an unfavorable genetic background (Figure 1).

In this review, we discuss the current knowledge concerning the impact of lifestyle in the progression of metabolic disorders and the onset of hypogonadism, with a focus on the genetic and epigenetic basis underlying this association. Our goal is to trace lifestyle recommendations towards prevention,

improvement and reversal of hypogonadism. Additionally, we discuss the efficacy and relevance of lifestyle interventions for the individual, and the potential inter and transgenerational effects. A literature search was performed in March and April 2020 giving preference to papers published since 2010. MeSH terms were used as input in Google Scholar and Pubmed search engines whenever possible. Search terms included, but were not limited to, “hypogonadism genetics”, “metabolic disorder hypogonadism”.

2. Metabolic disorder and hypogonadism

2.1. Metabolic diseases

Obesity and T2D are amongst the most prevalent non-communicable diseases (NCDs) worldwide (World Health Organization, 2014). These metabolic diseases share etiologies, notably those related to lifestyle such as unhealthy food habits and low levels of physical activity (World Health Organization, 2000, World Health Organization, 2016), despite their different characteristics. Obesity is defined by a Body Mass Index (BMI) equal to or higher than 30 kg/m^2 (World Health Organization, 2000). T2D is a metabolic disease characterized by the presence of chronic hyperglycemia that results from a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (American Diabetes Association, 2009, World Health Organization, 2016), and requires several criteria to be met to be diagnosed. There are also relevant non-pathological conditions related to obesity and T2D which have been implicated with the onset of metabolic disease and comorbidities. Overweight is defined as the BMI score equal or over 25 up to 30 kg/m2 (World Health Organization, 2000), whilst metabolic syndrome (MetS) is defined as a cluster of risk factors

towards T2D and cardiovascular disease (International Diabetes Federation, 2006). Pre-diabetes is another T2D-related condition, in which individuals present just some of the criteria to be diagnosed with T2D (World Health Organization, 2016).

Metabolic diseases have been widely associated with endocrine dysfunction (Alves et al., 2016, Crisóstomo et al., 2018, Jesus et al., 2017, Monteiro and Batterham, 2017, Rato et al., 2016), including secondary hypogonadism and LOH (Khera et al., 2016, Morales and Lunenfeld, 2002, Wang et al., 2009). Present figures indicate that hypogonadism is found in at least 20% of men suffering from T2D (Al Hayek et al., 2017, Dhindsa et al., 2016, Ho et al., 2015, Malipatil et al., 2019). Regardless of the underlying metabolic disease, the progression towards hypogonadism in adult males follow common pathways, related to endocrine regulation (Figure 2). The key events in this progression are the negative feedback over the HPG axis, impaired steroidogenesis, cell metabolic reprogramming and insulin resistance/insufficiency.

Several animal studies suggest that insulin can mediate the secretion of pituitary hormones through the stimulation of GnRH hypothalamic neurons, triggering GnRH synthesis and secretion on the hypothalamus (Burcelin et al., 2003, Kovacs et al., 2002, Navratil et al., 2009). Thus, insulin resistance or insufficiency caused by progressive stages of T2D affect GnRH release. Despite the lack of clinical evidence concerning hypothalamic insulin resistance, studies conducted in rodents have related the excessive intake of fatty acids with the onset of insulin resistance in the hypothalamus (Benoit et al., 2009, De Souza et al., 2005). In these works, the phosphorylation of a regulatory serine of the insulin receptor and the insulin receptor substrate-2, via c-Jun N-terminal

kinase and Protein Kinase C-θ, was the proposed mechanism. Another mice study demonstrated that the knock-out of the insulin receptor in neurons leads to a decline in LH release by the pituitary gland, despite elevated serum insulin levels (Brüning et al., 2000). Consequently, FSH and LH levels decrease, and the steroidogenic function of LCs is not stimulated. In turn, in the presence of low T levels, adipogenesis from mesenchymal stem cells and fatty acid uptake by adipocytes increases. Ultimately, the enlarged adipocyte highly expressing P450 aromatase converts T into estradiol (E_2), which exerts negative feedback over LH release (Cohen, 1999, Corona et al., 2011, Simpson and Mendelson, 1987). High leptin levels secreted by the increased adipose tissue mass is also able to inhibit T production (Amjad et al., 2019, Isidori et al., 1999). Moreover, the dynamic remodeling of adipose tissue and excessive fatty acid storage, promotes local pro-inflammatory responses that elevate circulating TNFα and other adipokines levels that exert inhibitory effects on hypothalamic GnRH release and pituitary LH release (Corona et al., 2011, Dandona and Dhindsa, 2011). Leptin stimulates the pancreas to secrete insulin, while both insulin and fat accumulation inhibit Sexual Hormone Binding Globulin (SHBG) synthesis by the liver, decreasing SHBG-bound T (Pasquali et al., 1995). Although this results in a transient increase in free T, the net yield of free T is negative, as it is responsible for activating feedback mechanisms that inhibit T production by LCs (Pitteloud et al., 2005). Finally, increased adipose tissue fat accumulation and elevated leptin levels will aggravate insulin resistance, and further stimulate the pancreas to secrete insulin, whereas potentiating the risk of endocrine pancreas secondary failure.

Leptin decreases human SCs acetate production and was proposed to be a regulator of spermatogenesis nutritional support by (Martins et al., 2015). Furthermore, leptin concentrations within normal physiological ranges increase glucose transporter 2 (GLUT2) protein expression and lactate dehydrogenase (LDH) activity in human SCs, suggesting increased lactate production (Martins et al., 2015). In another study, ghrelin was demonstrated to modulate human SCs metabolic phenotype, by decreasing glucose consumption and mitochondrial membrane potential. Interestingly, LDH activity and lactate production remained unaltered. These results suggested that ghrelin could act as an energy sensor in human SCs in a dose-dependent manner (Martins et al., 2016). Moreover, GLP-1 was shown to increase SCs lactate production and decrease protein carbonylation, without affecting mitochondrial functionality (Martins et al., 2019). Energy status-related hormones are recognized to contribute to hypogonadism development, although the mechanisms are not entirely characterized. The obesity-related increase of T aromatization into E_2, boosting the negative feedback loop between the testis and the hypothalamus was one of the first mechanisms to be proposed. E_2-mediated GnRH pulses disruption (Polari et al., 2015) is further impaired by leptin resistance, a common obesity trait (Considine et al., 1996, Frederich et al., 1995), which contributes to decrease serum T (Moschos et al., 2002). Leptin indirectly regulates GnRH secreting neurons function through afferent neurons (Quennell et al., 2009). Altogether, the abovementioned effects downregulate pituitary hormones (LH and FSH) secretion, ultimately leading to HPG axis disruption. Concomitantly, as a result of obesity-associated chronic inflammatory status, high circulating levels of inflammatory cytokines, including tumor necrosis factor TNF-α are

observed (Moon et al., 2004). Cytokines can induce a severe decrease in T production by LCs (Bornstein et al., 2004). Moreover, TNF-α was reported to inhibit steroidogenic acute regulatory (StAR) protein expression in mouse LCs (Budnik et al., 1999). StAR, responsible for cholesterol transport into mitochondria, is a rate-limiting enzyme of T steroidogenesis (Wang et al., 2017). Additionally, TNF-α administration (50 μg/m^2 for 3 weeks) was reported to significantly reduce T production in humans, further supporting the influence of obesity-related inflammatory state on the steroidogenic machinery (van der Poll et al., 1993).Overall, these data highlight the intimate relationship between metabolic status and reproductive function, and the potential of metabolic abnormalities to induce reproductive disorders. Significant shifts in energy-related pathways, antioxidant defenses and amino acid metabolism were also reported in mice with MetS induced by a high-fat diet (Crisóstomo et al., 2019). In the presence of MetS, several sperm parameters were observed to be affected, notably sperm motility, viability and morphology, illustrating the influence of metabolic disorders on testicular tissue. In rats fed with high-energy diets, pre-diabetes was also demonstrated to alter testicular mitochondrial bioenergetics and oxidative stress, by inhibiting the PGC-1α/Sirt3 axis (Rato et al., 2014). Notwithstanding, the association between hypogonadism and metabolic disease is bidirectional, *i.e.*, the onset of hypogonadism is a risk factor towards metabolic disease (Dandona and Dhindsa, 2011). On a longitudinal study in adult men, low serum T levels were found to be predictors of MetS (Corona et al., 2009, Corona et al., 2011). Other studies have advocated that low T and SHBG levels are associated with increased risk of

metabolic disorders in non-overweight middle-aged men (Kupelian et al., 2008, Kupelian et al., 2006).

2.2. Inborn defects of metabolism

Inborn defects of metabolism due to chromosomal and genetic defects can be a cause of hypogonadism. One such genetic cause is the kisspeptin receptor defects (Kiss1r, formerly known as GPR54) (De Roux et al., 2003, Oakley et al., 2009). Kisspeptin is a neuropeptide produced by specialized neurons in the hypothalamus that stimulates GnRH production by GnRH-producing cells, and consequently LH and FSH release by the pituitary gland. The pulsatile secretion of GnRH in response to kisspeptin, is regarded as the hallmark of puberty in mammals. The roles of kisspeptin in brain and reproduction were extensively reviewed by (Oakley et al., 2009), and more recently by (Clarke et al., 2015) and (Comninos and Dhillo, 2018).

Kallman's Syndrome characterized by hyposmia or anosmia and hypogonadism due to GnRH deficiency is another example of a genetic disease, which can result from several identified monogenic mutations, such as Kal1 (Kim, 2015, Stamou and Georgopoulos, 2018). Yet, neither anosmia nor hypogonadism are invariably found in Kallman's Syndrome, as different mutations result in distinctive phenotypes that sometimes overlap (Kim, 2015, Quaynor et al., 2016). Klinefelter Syndrome (KlS) is the most frequent sex chromosome disorder, occurring in individuals that most often present a 46, XXY karyotype, among several other related chromosomal abnormalities (Smyth and Bremner, 1998). KIS has an estimated prevalence of 1.72 cases per 1,000 male live

births worldwide (Morris et al., 2008). Men with this syndrome exhibit characteristic phenotypic features, gonadal dysgenesis with abnormal spermatogenesis, oligo or azoospermia, sexual dysfunction and elevated serum FSH and E2 levels (Bonomi et al., 2017, Smyth and Bremner, 1998). However, KIS prevalence is likely underestimated, as individuals with milder KIS features can be easily missed or misdiagnosed (Bonomi et al., 2017, Morris et al., 2008, Smyth and Bremner, 1998). (Bernardino et al., 2016) demonstrated that the GPR30 receptor was the most expressed E2 receptor in testes of KIS patients and presented a 12-fold increase in contrast to the ERβ receptor that is the most expressed E2 receptor in testes of men with normal karyotype. E2 exerts a negative feedback on the HPG axis and inhibits pituitary LH release, thus contributing for hypogonadism. Moreover, GPR30 activation by E2 inhibits steroidogenesis in LCs (Vaucher et al., 2014). Therefore, persistent high E2 levels found in KIS patients further inhibit T production by LCs via GPR30-related pathways overstimulation.

In addition to chromosomal abnormalities and mutations directly responsible for causing hypogonadism, other genetic and epigenetic factors associated with a genetic predisposition for metabolic disorders can also affect the HPG axis and should not be overlooked. Prader-Willi (Butler, 2011) and Bardet-Biedl (Forsythe and Beales, 2013) are two examples of syndromic obesity associated with hypogonadism. These syndromes are also associated with mental retardation, dysmorphic features and organ-specific abnormalities (Huvenne and Dubern, 2014). In 1997, a prohormone convertase 1 gene frameshift mutation, responsible for the creation of a premature stop codon causing a defective prohormone processing, was described as the first human single

genetic defect that leading to severe obesity without developmental delay in rodents and humans (Jackson et al., 1997). In the same year, the single guanine nucleotide deletion in the leptin gene was also reported to be associated with severe obesity, reinforcing the key role of leptin in regulating energy balance (Montague et al., 1997). This deficit in leptin causes pubertal delay associated with hypogonadism (Farooqi, 2002). Fortunately, in this case, the administration of exogenous leptin has proven to be effective to attenuate the manifestations of this inborn error (Farooqi, 2002). Notably, the most frequent cause of monogenic obesity are mutations in genes associated with the leptin/melanocortin axis that regulates food intake (Nóbrega and Rodriguez-López, 2014). These mutations can either occur *de novo* in subjects with no previous family background or inherited, usually according to Mendelian Laws in a similar way as other monogenic disorders (World Health Organization, 2017). So far, more than 20 single-gene autosomal disorders were described as causing human obesity and these genes are classified as obesity-related genes (O'Rahilly, 2009).

As previously stated, obesity and T2D can be associated with hypogonadism and vice-versa. As the obesity epidemic reaches alarming proportions, more children are born from overweight/obese parents. Thus, future generations are at greater risk of inheriting deleterious epigenetic traits that can trigger the development of metabolic disorders (Reynolds et al., 2013) and, consequently hypogonadism, later in life.

3. Lifestyle factors

3.1. Diet and body weight

Excessive energy intake can lead to excessive adiposity, obesity and consequently hypogonadism. Obesity-related hypogonadism can be reverted by weight loss interventions, such as bariatric surgery (Pellitero et al., 2012). Obesity surgery results in significant and sustained weight loss and promotes several other positive effects including overall improvement of metabolic health. Indeed, weight loss was shown to improve total and free T in a meta-analysis by (Corona et al., 2013), regardless of being achieved via dietary intervention or bariatric surgery. Nevertheless, bariatric surgery was more effective than dietary interventions in increasing total T (8.73 nmol/l vs 2.87 nmol/l, respectively), which the authors attributed to the greater percentage of weight lost (bariatric surgery - 32%; lifestyle intervention - 9.8%). Moreover, data from the selected RCTs show that total T is positively correlated with the percentage of weight lost, and it is even more effective in men at younger ages, non-diabetic and more severe obesity degrees. Weight loss was shown to be the most relevant factor to attenuate or even revert the hypogonadal state, and has therefore been highlighted as the main target of treatment intervention in several longitudinal studies and even clinical guidelines (Camacho et al., 2013, Khera et al., 2016, Niskanen et al., 2004, Rastrelli et al., 2018). This assumption was further supported by The European Male Aging Study (EMAS), which identified a body mass index (BMI) reduction of over 15% to be required to normalize total T, free T and LH serum concentrations in men aged between 40-79 years old (Camacho et al., 2013, Rastrelli et al., 2018). Unfortunately, less than 1% of the EMAS study subjects achieved that degree of weight loss (Camacho et al., 2013, Khera et al., 2016). More recently, the effect of lifestyle intervention

aimed to achieve 10% weight loss was assessed in a clinical trial conducted in 14 men in obesity-related hypogonadism (De Lorenzo et al., 2018). After intervention, total T levels significantly increased (300.2 ng/dL vs. 408.3 ng/dL) and E2 levels significantly decreased (48.3 pg/mL vs. 39.2 pg/mL) compared to baseline (De Lorenzo et al., 2018). To overcome the limitation related to the difficulty of achieving the weight loss threshold required to improve hypogonadism, the use of Testosterone Replacement Therapy (TRT) in combination with diet and exercise was proposed (Heufelder et al., 2009). The rationale was that T promotes adipose tissue mass reduction whereas increasing muscle mass, therefore TRT was likely to potentiate weight loss driven by lifestyle intervention. After 52-weeks of lifestyle intervention combined with TRT, there was a significant decrease in waist circumference, glycaemic control and MetS improvement when compared to placebo (Heufelder et al., 2009). Although, whether T levels were regularized after ceasing the treatment is unknown. TRT alone has been recommended to hypogonadal obese men. Several long-term follow-up studies (5-11 years) report that hypogonadal obese men taking testosterone undecanoate injections every 3 months have shown a significant reduction in body weight, waist circumference and BMI (Francomano et al., 2014, Saad et al., 2020, Saad et al., 2016). Yet, although (Francomano et al., 2014) report improvements in the metabolic profile of these men, none of those studies report an hormonal normalization after ceasing TRT.

3.2. Physical activity

Even mild physical activity, when combined with diet and antidiabetic drugs, notably metformin, can result in significant hypogonadism improvement (Casulari et al., 2010). (Grossmann, 2011) further advocates the adoption of mild physical exercise in men with T2D and hypogonadism before considering prescribing TRT. (Grossmann and Matsumoto, 2017) also defend that even mild exercise provides sufficient improvement of overall health to prevent the onset of hypogonadism in middle-aged and older men. This recommendation is supported by studies where mild exercise was demonstrated to alleviate MetS manifestations (Pattyn et al., 2013) and promote significant weight loss (Khoo et al., 2013). The exercise volume and intensity also influence the outcomes of an exercise program. (Khoo et al., 2013) assigned 75 sedentary men with obesity and hypogonadism either to a low-volume (<150 minutes/week) or a high-volume (200–300 minutes/week) moderate-intensity exercise program (24 weeks long). The exercise was prescribed along a dietary intervention to reduce daily caloric intake by *circa* 400 kcal. T levels increased 2.6 times more (2.06 ± 0.46 nmol/L) in the high-volume group than in the low-volume group (0.79 ± 0.46 nmol/L), who also lost almost twice the weight (-5.9 ± 0.7 kg vs. -2.9 ± 0.7 kg). Thus, leading to conclude that regardless of the type of intervention used to achieve it, weight loss is pivotal for hypogonadism improvement.

Despite the previously mentioned preponderance of weight loss in conveying beneficial effects in HH condition, the therapeutic potential of physical exercise in HH has also been demonstrated, though only in animal models. A study using rabbits as a model reported improvements in GnRH expression, increase LH levels and T production and even overcome erectile dysfunction, after a

progressive physical exercise program (Morelli et al., 2019). In this study, animals were fed either by a regular diet or a high-fat diet (regular diet enriched with 0.5% cholesterol and 4% peanut oil) during 12 weeks and, simultaneously, a subset of animals in each group underwent a physical exercise program. The animals fed with a high-fat diet and which have not undergone physical activity developed MetS, hypogonadism, erectile dysfunction and elevated pro-inflammatory markers in testis and hypothalamus, whereas their exercising counterparts had similar parameters as controls. No significant changes in body weight were reported. Accordingly, physical exercise revealed as a potentially effective lifestyle intervention to attenuate hypogonadism symptoms and prevent its onset, independently from weight loss, in animal models. In addition to the physiological differences of these animal models and humans, the former do not account for subjective variables as the resilience needed to keep an exercise and diet plan.

3.3. Environmental contaminants

Environmental contaminants comprehend a broad range of substances that may have a significant impact on the HPG axis and reproductive function either by acting as steroid analogs (*e.g.* obesogens, endocrine disruptors) either by cell-specific toxicity in endocrine organs (*e.g.* hydrocarbons, heavy metals) (Cardoso et al., 2017, Diamanti-Kandarakis et al., 2009, Gabrielsen and Tanrikut, 2016, Stuppia, 2019). Endocrine disruptors are exogenous compounds, natural or human-made, with the ability to interact with endocrine receptors, altering signaling pathways and culminating in the disruption of the endocrine system. These compounds can be classified as non-steroid or steroid

analogs, accordingly to its chemical structure (Diamanti-Kandarakis et al., 2009).

Obesogens are a group of endocrine disruptors that can promote adipogenesis and lipid accumulation (Grün and Blumberg, 2009). Obesogens usually are structurally similar to sex steroids with the ability to interact with the HPG axis leading to reproductive dysfunction. Furthermore, a large portion of these compounds is lipophilic, creating a vicious cycle, where fat accumulation becomes a way to further accumulate endocrine disruptors, which aggravates the endocrine imbalance already established by obesity (Grün and Blumberg, 2009). Men are often exposed to different classes of environmental contaminants or occupational hazards that may contribute to hypogonadism (Gabrielsen and Tanrikut, 2016). Besides that, endocrine disruptors and obesogens can steadily accumulate in the human body (Cardoso et al., 2017). Processed foods, food packaging, herbicides/pesticides and animal hormones are well-described sources of both endocrine disruptors and obesogens (Cardoso et al., 2017). Due to its large variety, it is difficult to identify the specific mechanism by which each of these compounds promote hormonal imbalances. A study in fish revealed that organotin compounds, used as plastic stabilizers and in paint, inhibit the activities of CYP450, CYP1A1 and aromatase (Fent and Stegeman, 1991). These enzymes are present in several tissues and participate in the synthesis of several hormones, including sex hormones (E_2 and T), thyroid and retinoid hormones (Fent, 2003). Organotin compounds are also obesogens, able to activate nuclear receptors and stimulate adipocyte differentiation (Grün and Blumberg, 2007). Organotin compounds appear to have a direct impact on the HPG axis, by affecting the synthesis of sex

hormones. Other obesogens may indirectly affect the HPG axis by promoting obesity which, in turn, will promote hormonal dysregulation. In this category are included persistent organic pollutants, such as dichloro diphenyl trichloroethane (DDT), and heavy metals, such as lead, among several others (González-Casanova et al., 2020). DTT is reported to increase adipocyte differentiation, while promoting the expression of peroxisome proliferator-activated receptor-gamma and other markers of proadipogenic activity (Howell and Mangum, 2011, Strong et al., 2015). Similarly, lead was reported to have a proadipogenic action in 3T3-L1 cells, an adipocyte like cell line, by a mechanism that involves the activation of peroxisome proliferator-activated receptor-gamma (Martini et al., 2018). Lead exposure in rats also stimulates the differentiation of mesenchymal cells into mature adipocytes (Beier et al., 2013). In sum, the action of several environmental contaminant compounds can directly, or indirectly, promote HPG dysregulation.

3.4. Substance abuse

Opioids abuse can directly induce hypogonadism. Endogenous opiates (endorphins) inhibit T synthesis by direct action on testicular LC to inhibit steroid hormone production and hypothalamic neurons to inhibit GnRH release (Daniell, 2002). Methadone and orally-consumed synthetic endorphins are also reported to decrease total LH levels and consequently total T levels (Daniell, 2002). As an opiate, methadone can exert the same inhibitory effect over GnRH release as endorphins, thus both methadone and synthetic endorphins exacerbate the effect of endogenous endorphins and impair the HPG axis.

Accordingly, men consuming 100 mg of methadone a day, for pain relief or treatment of heroin addiction, were found to present subnormal total T or E2 levels (Daniell, 2002). Additionally, sexual dysfunction arises in 87% of men after starting opioid therapy.

Alcohol and tobacco, although widely legalized and consumed, are also linked to hypogonadism (Gabrielsen and Tanrikut, 2016). Alcohol was demonstrated to suppress the HPG axis in mice and humans (Emanuele and Emanuele, 1998), besides having direct toxic effects on testicular LCs and SCs (Jang et al., 2002). In frequent drinkers, SHBG availability is improved when alcohol intake is reduced (Camacho et al., 2013), which consequently improves T bioavailability. Conversely, anticonvulsants can induce hypogonadism through overexpression of SHBG, thus reducing free T availability (Corona et al., 2011, Mazdeh et al., 2020). The deleterious effects of anticonvulsants in endocrine functions and most particularly on the HPG axis, are reported since the 1970s, although the underlying mechanisms are still not fully understood (Isojärvi et al., 2005). Several anticonvulsants can promote SHBG synthesis by the liver, reducing T bioavailability (Isojärvi et al., 2005). Valproic acid can affect GnRH release (and consequently LH and FSH) as it modifies GABAergetic transmission (Isojärvi et al., 2005).

Nonetheless, anabolic steroids are among the most common threats to normal HPG. Anabolic steroid drugs are molecule analogs synthetically produced to mimic the chemical structure and physiological effects of steroid hormones. Synthetic T or androgen analogs are often consumed by bodybuilders, sportsmen, or simple gym enthusiasts as a mechanism to improve physical performance, promote muscle hypertrophy and hyperplasia and reduce fat

mass (El Osta et al., 2016, Jarow and Lipshultz, 1990). However, anabolic steroids also exert a negative feedback over the GnRH pulsatile secretion, thus inhibiting LH and FSH release and disrupting normal HPG axis (El Osta et al., 2016, Jarow and Lipshultz, 1990). (Rahnema et al., 2014) in a meta-analysis that comprised data from men who had taken and ceased taking anabolic steroids for non-pathological purposes, follow-up studies published between 1965 and 2013, concluded that even after anabolic steroid drugs withdrawal, total serum T levels were on pair with agonadal men. Younger men were found to be more capable to recover normal HPG axis after drug cessation, therefore illustrating that the HPG axis of younger men is more dynamic and adaptable. Other factors linked to a quicker recovery of normal HPG axis were the use of lower anabolic steroid doses over shorter durations, and higher T levels at baseline (Rahnema et al., 2014).

4. Temporary, permanent and transgenerational effects of lifestyle in hypogonadism

The lifespan of environmental factors that potentially lead to hypogonadism can be very broad (Figure 3). The effect of some factors (toxicants, diet) can be readily reversible after discontinuing the exposure or modifying lifestyle habits. In contrast, the effects of other environmental factors can be more silent, imprinted and irreversible. To what extent these effects can be reversed is also influenced by the duration and intensity of exposure. The effects of lifestyle interventions were demonstrated to be self-limited effects in mitigating hypogonadism, notably in men over 50 years old with obesity (Grossmann and

Matsumoto, 2017). Moreover, the available data also support that lifestyle interventions are difficult to manage and to maintain, limiting the long-term success. Thus, diet and exercise promote weight loss and can potentially revert hypogonadism (Grossmann and Matsumoto, 2017), although depending on the commitment and the observed effects are usually limited to the duration of the intervention. More recently the role of environmental factors in modulating epigenetic traits transmitted to the offspring has also been highlighted. This so-called intergenerational (father-son) and transgenerational (grandfather-grandson) inheritance has been implicated in the etiology of several non-communicable diseases, notably obesity and T2D (Skinner, 2008). A classic example of intergenerational epigenetic inheritance is uniparental disomy (UPD) of imprinted genes (Stuppia, 2019). This epigenetic mechanism consists of the inheritance of both copies of the same allele from the same progenitor. Prader-Willi Syndrome (PWS) is a genetic disease that results from the loss of function of paternally imprinted genes in chromosome 15 (15q11-q13), and patients typically present both obesity and hypogonadism (Cassidy et al., 2012, Stuppia, 2019). In 1-3% of PWS cases, the defect originates in spermatogenesis which impair the methylation pattern of the imprinted genes in the 15q11-q13 region of the offspring (Cassidy et al., 2012, Glenn et al., 1997). Interestingly, reports from the late ’80s found PWS to be more frequent in the offspring of men exposed to hydrocarbons (Cassidy et al., 1989, Strakowski and Butler, 1987), suggesting a role for these environmental toxicants in the intergenerational inheritance of disease. More recently, another group also reported the role of hydrocarbons in the intergenerational inheritance of sperm defects and the transgenerational inheritance of obesity in rats (Tracey et al., 2013). In this

study, gestating females (F0 generation) were exposed to jet fuel JP-8 via intraperitoneal injection during the period of fetal gonadal development (embryonic day 8 to 14). The male lineage of those females (F1 generation) presented azoospermia, seminiferous atresia, apoptotic spermatogenic cells, atrophic prostatic ductular epithelium and delayed pubertal onset. In turn, male rats of the first transgenerational generation (F3 generation), presented obesity and 33 sperm epimutations, thus demonstrating the paternal transmission of molecular fingerprints caused by environment toxicants.

Paternal obesity and T2D have been linked to the onset of metabolic disorder in the direct male progeny (sons) but also in subsequent generations (grandsons and subsequent descendants). This data has been mostly supported by animal models, but also by large-scale longitudinal studies in human populations (Kaati et al., 2002, Painter et al., 2008). One of the mechanisms proposed to be involved in the inter and transgenerational inheritance of metabolic disorder is the modulation of the neural reward pathways (Bays and Scinta, 2015). Neural reward pathways are related to satiation and play an important role in appetite regulation. Ancestral inheritance of obesity via this mechanism has been previously reported in rodent models (Bays and Scinta, 2015, Youngson and Morris, 2013). Notably, (Donkin et al., 2016) reported significant differences in the miRNA content in the sperm of obese men after bariatric surgery. Besides, the miRNAs differentially expressed before and after surgery were implicated in the embryonic neural development, thus the nutritional status of the father, at conception, can be pivotal in the neural development of the embryo. More recently, (Nätt et al., 2019) reported that the tsRNA content in human sperm shows rapid responses to diet. Therefore, even short-lasting lifestyle changes

can modulate the health outcomes of the progeny. Another study has shown that high-fat diet-induced obesity in rodents can modulate metabolic health via parental lineage for up to two generations (Fullston et al., 2013).

Environmental toxicants can also induce persistent effects over several generations. In a rat model, DDT exposure was found to induce obesity in the great-grand-children (F3) generation, in both males and females (Skinner et al., 2013). The experimental model consisted of (Tracey et al., 2013): F0 gestating females were intraperitoneally injected with DDT 50 (high-dose) or 25 (low-dose) mg per kg body weight per day, or DMSO vehicle (control), during embryonic days 8 to 14. The incidence of obesity in F3 males (great-grand-children of F0 females, and first transgenerational generation) was significantly higher in the descendants of the DDT-exposed F0 females (High-dose: 75%; Low-dose: 50%; Control: 22.5%). Besides, in the same generation, the descendants of F0 females exposed to the highest DDT concentration had the highest incidence of testis disease (50%), the highest proportion of apoptotic germ cells per tissue section (60% of apoptotic germ cells per section) and the lowest sperm counts (85% of the Control) (Skinner et al., 2013). Similarly to ancestral hydrocarbon exposure, several epimutations were identified in the sperm of F3 generation, caused by differential DNA methylation regions (DMRs). The same research group, using a similar approach, found similar effects caused by Bisphenol A (BPA) and other plastic derivatives (Manikkam et al., 2013). In this study, the researchers injected the gestating rats with a mix of plastic derivates (BPA 50 mg/kg BW/day, DEHP 750 mg/kg BW/day and DBP 66 mg/kg/BW/day), a lower dose of plastic derivates (half the concentration of the previous group) or DMSO (the control). Interestingly, the males of F3

generation originated from the lower plastic dose lineage presented the higher percentage of transgenerational testis disease (40%). Although plastic derivates did not cause as much reproductive and metabolic transgenerational damage to male rats as hydrocarbons or DDT, they have induced the highest number of epimutations at DMRs (197).

5. Conclusions

Male hypogonadism can result from a complex interaction between lifestyle, metabolic health and genetic background. The physiological mechanisms involved in the onset of obesity-related male hypogonadism create an intricate vicious cycle that is difficult to break. Lifestyle interventions can improve hypogonadism, but are limited in terms of effectiveness and temporal persistence, while the sole intervention that proved to have significant and long-lasting success was bariatric surgery. Additionally, the gonadal effects of metabolic disorders and other environmental factors, are not only deleterious for the individual, but can also harm the progeny of future generations. Therefore, it is crucial to prevent and treat men affected with these conditions to avoid the perpetuation of the disease in the offspring, and before it becomes a one-way ticket for human health.

Author contributions

LC and SCP performed the bibliographic search and wrote the manuscript. LC illustrated the images. MPM, JFR, PFO and MGA critically revised the manuscript. All authors approved the final version of this manuscript.

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Figure legends

Figure 1: The triad of Hypogonadism. The genetic background may be crucial for the onset of any disease. Nevertheless, the onset of a chronic metabolic disorder, such as T2D, and the perpetuation of unhealthy lifestyle choices, greatly increase the risk for developing hypogonadism as a comorbidity.

Figure 2: Simplified schematic representation of the links between metabolic disease and hypogonadism. The progression of male hypogonadism associated with metabolic disease lies in a complex network of metabolic and endocrine pathways. However, HPG axis dysfunction, impaired steroidogenesis, cell metabolic reprogramming, and insulin resistance/insufficiency are key variables in this equation. Thus, those are potential therapeutic targets to halt the progression of the disease.

Figure 3: Lifespan of environmental factors that interfere in gonadal function. The effect of diet and exercise tends to be limited to the duration of the intervention. Still, the nutritional status of a man at the time of conception can modulate the predisposition for metabolic disorders and hypogonadism in subsequent generations. Environmental toxicants can also modulate the predisposition for metabolic disorders and hypogonadism in several generations, through epigenetic changes carried by sperm.

Table 1: Male hypogonadism etiologies grouped by type and hypogonadism classification.

	Classification	
Origin	**Primary**	**Secondary**
Organic	Klinefelter Syndrome Cryptorchidism Cancer (*e.g.* testicular/scrotal) Chemotherapy Testicular irradiation/damage Orchidectomy Orchitis Testicular trauma, torsion Advanced age[a]	Cancer (*e.g.* hypothalamic/pituitary) Iron overload syndromes Infiltrative/destructive disease of hypothalamus/pituitary
Functional	Prescription drugs (*e.g.* anticonvulsants)[a]	Hyperprolactinemia Alcohol, tobacco, cannabinoids[a] Opioids, anabolic steroids MetS, T2D[a] Overweight/Obesity[a] Excessive exercise Unbalanced diet Environmental contaminants[a]

[a] Mixed effects of primary and secondary hypogonadism. In these cases, the etiology was allocated according to its most representative classification. Adapted from Bhasin et al. (2010) and Bhasin et al. (2018).