Chapter 40

Obesity, sexual maturation and male reproduction

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ABSTRACT
Overweight and obesity are pandemic problems, occurring in high-, middle-, and low-income countries (particularly in urban areas), in both sexes, and in all age groups. Obesity can cause changes in the levels of sex hormones, in the spermatogenic process, and in sperm maturation, leading to reduced sperm quality, oligospermia, damage to DNA integrity, affecting sperm motility and capacitation, and therefore interfering in the fertilization process and in the quality of the embryo. Moreover, the increase in adipose tissue may cause elevated concentrations of sex steroids, adipokines, and leptin, as well as the aromatization of androgens into estrogens, which may accelerate the onset of puberty and, subsequently, the seminal quality and homeostasis of sex hormones in adulthood. However, the literature is contradictory about the effects of obesity on the onset of puberty, sperm and male fertility.

Keywords: Obesity, Male Reproduction, Puberty, Sperm.

1 INTRODUCTION

Obesity is a chronic metabolic disease caused by interactions of various genetic and environmental factors, and is considered a major public health problem today. It is characterized by increased adiposity, dyslipidemia, oxidative stress and inflammation and is associated with high morbidity and mortality, mainly from cardiovascular diseases and diabetes (MUST et al., 1999; KLEIN et al., 2004; AL-GOBLAN et al., 2014; CANTIELLO et al., 2015; HRUBY et al., 2016; MANDVIWALAet al., 2016; KACHUR et al., 2017). It is also related to other comorbidities, such as several types of neoplasms and chronic diseases, such as liver and gallbladder diseases, sleep apnea, depression, and infertility (CALLE et al, 2003; TARGHER & ARCARO, 2007; CARTER & WATENPAUGH, 2008; PETRY et al.; 2008; ROMERO-CORRAL et al., 2010; NARANG & MATHEW, 2012; RAJAN & MENON, 2017; AVGERINOS et al., 2019; COSTA et al., 2019; POLYZOS et al., 2019).

Obesity has gained prominence on the international public agenda, being characterized as an event of global proportions and increasing prevalence. In Brazil, overweight and obesity have been increasing in all age groups, in both sexes, and in all income levels. The Ministry of Health states that obesity, even though it is difficult to define, constitutes a public health problem, because according to data obtained by the 2019 National Health Survey, 41 million Brazilians aged 18 years and older are obese, which is

equivalent to approximately 20% of the country's total population, with more than half of the population already overweight (IBGE, 2019).

According to data from the World Health Organization, the prevalence of overweight and obesity in children and adolescents worldwide has increased tenfold over the past four decades (ABESO, 2017). In addition to genetic aspects, inadequate eating habits and sedentary lifestyle are usually recognized as the main factors contributing to the current obesity epidemic. However, the magnitude of the phenomenon indicates that other factors, which are underestimated, may influence overweight and the occurrence of obesity.

Environmental stimuli or insults during critical periods of development can cause long-term effects. Metabolic programming occurs at critical periods in the body's development, among which are the gestational period, breastfeeding phase, early childhood phase and the puberty phase. Such periods are characterized by greater proliferation, differentiation, growth, and high cellular plasticity (SOCIEDADE BRASILEIRA DE PEDIATRIA, 2012; ABESO, 2016). The neonatal period is a vulnerable phase to nutritional changes, which can cause physiological modifications and in the programming of the mechanisms involved in the regulation of energy metabolism throughout life, with consequences that manifest only in adulthood (HABBOUT et al., 2013; MANDY & NYIRENDA, 2018; ARIMA & FUKUOKA, 2020).

The adipocytes of the unilocular (white) adipose tissue, besides storing triglycerides, synthesize and release hormones, lipokines, pro- and anti-inflammatory cytokines (adipokines) and exosomes containing microRNAs (miRNA), which are involved in the control of gene expression in other tissues, intra- and inter-tissue cell communication to regulate energy homeostasis, and the secretion of pro-inflammatory cytokines that result in insulin resistance (THOMOU et al., 2017). Adipokines, which include leptin, adiponectin, resistin, chemerin, and retinol-binding protein type 4 (RBP4), regulate metabolic homeostasis and are involved with the establishment of a chronic low-grade inflammatory state. Adipokines are also involved in insulin resistance and glucose metabolism in energy deficiency states. The accumulation of adipose tissue is accompanied by elevated leptin levels, decreased expression of soluble leptin receptors, and reduced leptin transport across the blood-brain barrier, determining reduced leptin signaling in the hypothalamus, which results in hyperleptinemia and leptin resistance. On the other hand, adiponectin levels are reduced in obese or insulin-resistant humans and rodents (MEIER & GRESSNER, 2004; KAWWASS et al., 2015; MATHEW et al., 2018; XIAO et al., 2020).

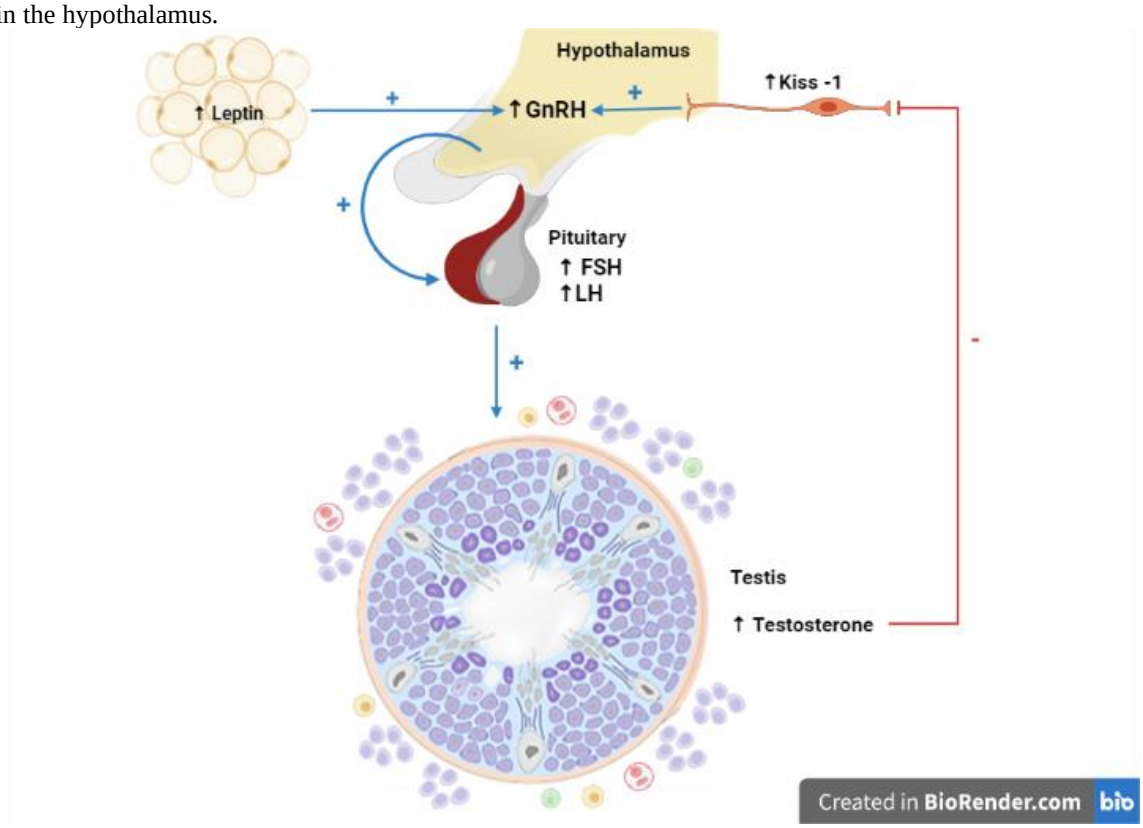
2 OBESITY AND THE ONSET OF MALE PUBERTY

Leptin is involved in the control of the hypothalamic-pituitary-gonadal (HHG) axis (HALAAS et al., 1995; ROSENBAUM & LEIBEL, 1998; BAILE et al., 2000 ; MISH et al., 2022). In the hypothalamus,

the indirect actions of leptin are mediated by the neuropeptide Kisspeptin-1 (Kiss-1), which in turn is involved in the onset of male puberty (OAKLEY et al., 2009; BENTSEN et al., 2010).

The function of the HHG depends on the spatio-temporal synchronicity of the development of hypothalamic neurons that synthesize and release gonadotropin-releasing hormone (GnRH). Pulses of GnRH are released by the hypothalamus during late fetal and early neonatal development, followed by a period of suppression of GnRH pulsatility until adolescence, when there is reactivation of GnRH release, the onset of puberty and reproductive maturation . The reactivation of GnRH neurons that occurs at the onset of puberty results from increased excitatory stimuli and decreased inhibitory signals. The Kiss-1 system and leptin constitute essential excitatory components for pubertal development (GRUMBACH, 2002). Kiss-1 stimulates hypothalamic neurons to release GnRH into the pituitary portal system and consequently activate and stimulate the secretion of gonadotropins, the initiation of the spermatogenesis process and the secretion of testosterone. GnRH neurons become more sensitive to Kiss-1 throughout postnatal development. A negative *feedback* mechanism is then established, in which increased testosterone levels inhibit Kiss-1 release by neurons in the arcuate nucleus and subsequently reduce GnRH secretion in the hypothalamus (Figure 1) (OAKLEY et al., 2009; SMITH & SPENCER, 2012; NIEUWENHUIS et al., 2020).

Figure 1. Schematic representation of the reactivation of the HHG axis at the onset of male puberty. The Kiss-1 system and leptin stimulate the reactivation of GnRH neurons, stimulating the secretion of pituitary gonadotropins and subsequently testosterone. A negative *feedback* mechanism is established, in which increased testosterone levels inhibit Kiss-1 release and reduce GnRH secretion in the hypothalamus.



In addition to leptin, other hormones involved in energy and hormone homeostasis may act as potential modulators of puberty onset, such as ghrelin and adipocytokine (NAVARRO et al., 2007; CHENG et al., 2011; WAGNER et al., 2012).

The onset and progression of sexual maturation is associated with weight and body composition (HILL et al., 2013). Increased adipose tissue can cause elevated concentrations of sex steroids, adipokines and leptin, as well as aromatization of androgens into estrogens, which can accelerate growth in obese children. Activation of the HHG axis and the onset of male puberty are extremely sensitive to different endogenous and environmental signals, which may interfere late on hormonal homeostasis in adulthood (KENNEDY & MITRA, 1963; EBLING, 2005; FERNANDEZ-FERNANDEZ et al., 2006; HRABOVSZKY et al., 2010; HUSSAIN et al., 2015; HOLMGREN et al., 2021). Changes in fetal nutrition and dietary habits in infancy and may influence endocrine activity, potentially affecting reproductive axis maturation (MANFREDI-LOZANO et al., 2018).

Although obesity may contribute to early onset of puberty in females, the literature is scarce and controversial regarding the relationship between obesity and the timing of puberty onset in males, associating overweight with early, late, or no change in the age of puberty onset (SLYPER, 1998; WANG, 2002; BIRO et al, 2006; AHMED et al., 2009; WAGNER et al., 2012; MARCOVECCHIO & CHIARELLI, 2013; LEE et al., 2016; LUNDEEN et al., 2016; CHEN et al., 2017; LI et al., 2017; BRIX *et al.*, 2020; BUSCH et al., 2020; ECKERT-LIND et al., 2020; NIEUWENHUIS et al., 2020; PEREIRA et al., 2021).

Thus, developmental and maturation alterations of the HHG axis caused by obesity may correlate with early onset of puberty (KENNEDY & MITRA, 1963; FRISCH, 1980; BÖTTNER et al., 2004; FERNANDEZ-FERNANDEZ et al., 2006; BURT & MCCARTNEY, 2010; PLANT, 2015; SHALITIN & KIESS, 2017) and subsequently may negatively impact seminal quality, sex and gonadotrophic hormone homeostasis, and fertility in adulthood (DOHLE et al, 2003; PATTON & VINER, 2007; RODRIGUES et al., 2009; WAGNER et al., 2012; SANCHEZ-GARRIDO *et al.*, 2013; CHADIO & KOTSAMPASI, 2014; JENSEN et al., 2016; LAURIDSEN et al., 2016; SLIWOWSKA et al., 2018; WANG et al., 2018; WAGNER et al., 2020; SANCHEZ-GARRIDO *et al.*, 2022). Also, puberty is a period susceptible to obesity-induced changes in spermatogenesis (PASCOAL et al., 2022).

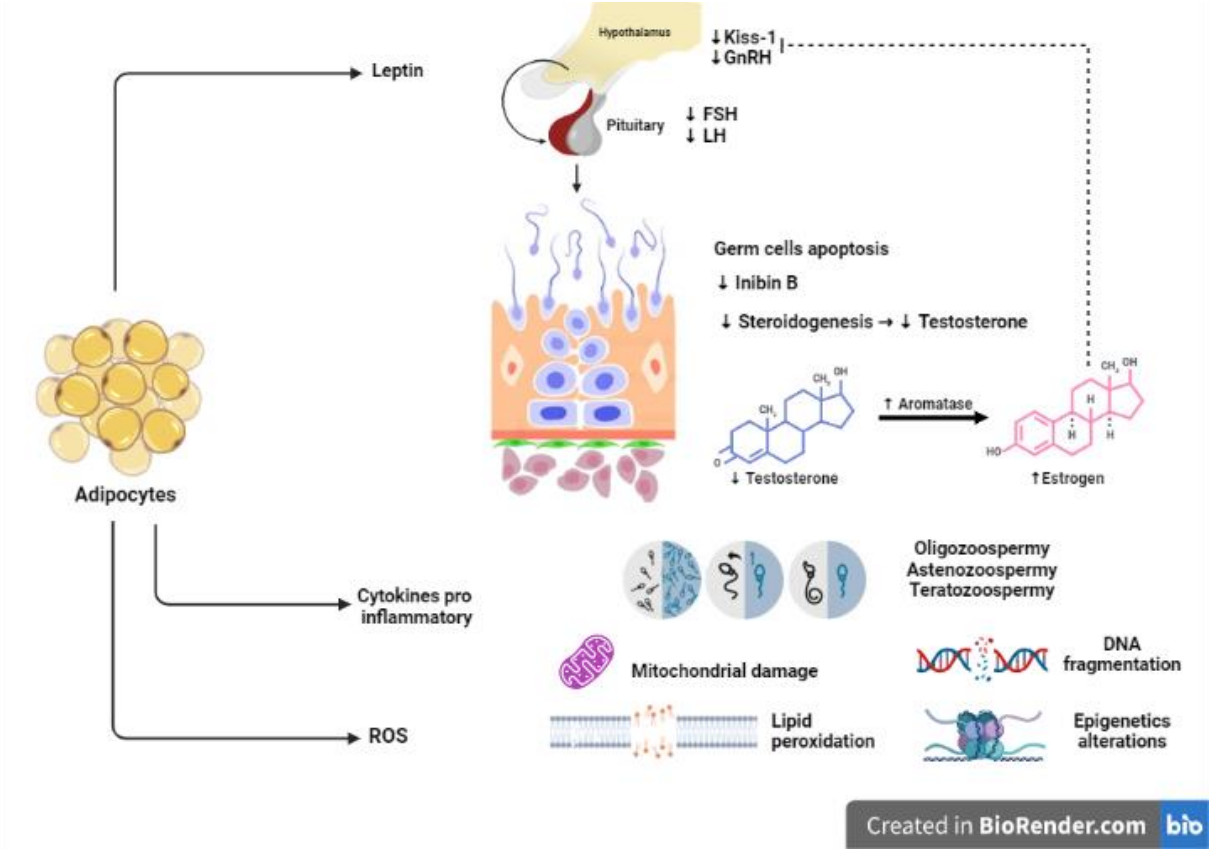
The proliferation of Sertoli cells that occurs during puberty determines an increase in inhibin-B. Obesity leads to impaired Sertoli cell proliferation and function and, as a result, reduced release of inhibin-B, interference with the HHG axis, spermatogenesis, and male reproductive function (WINTERS et al., 2006).

3 OBESITY AND MALE REPRODUCTION

The direct effects of obesity on the reproductive organs are not fully understood, are complex, and may negatively impact male fertility by several mechanisms, which include increased oxidative stress,

altered scrotal temperature related to adipose tissue distribution, and imbalance in the testosterone/ estrogen ratio, increased levels of inflammatory mediators, DNA fragmentation, and epigenetic changes in the spermatozoon, which culminate in damage to spermatogenesis, spermiogenesis, and sperm maturation, and therefore sperm quality (Figure 2) (CHAMBERS & ANDERSON, 2015; LEISEGANG et al., 2021; CARGNELUTTI et al., 2022).

Figure 2 - Schematic representation summarizing the effects of obesity on male reproduction. Obesity causes increased leptin production by adipose tissue, which in turn leads to alterations in the HHG axis, alteration in steroidogenesis and decreased testosterone production by Leydig cells, damage to the seminiferous epithelium, and reduced inhibin B biosynthesis by Sertoli cells. There is also an increase in aromatase levels leading to an increase in estradiol levels and a reduction in testosterone levels, which cause a reduction in Kiss-1 and GnRH levels in the hypothalamus, impacting the homeostasis of the HHG axis. Adipose tissue also promotes increased pro-inflammatory cytokines and ROS production, causing reduced sperm motility and concentration, damage to mitochondrial function, membrane lipid peroxidation, DNA fragmentation, and epigenetic changes in the spermatozoon.



Adipose tissue expresses components of enzyme complexes related to the activation, conversion and inactivation of these hormones, and is an important site for sex steroid metabolism and secretion. Several steroidogenic enzymes are expressed in adipose tissue, primarily cytochrome P450-dependent aromatase, 11β-hydroxysteroid dehydrogenase (HSD), and 17βHSD. Aromatase mediates the conversion of androstenedione to estrone and of testosterone to estradiol, while the 17βHSD enzyme converts sex steroids into more potent compounds, e.g. androstenedione to testosterone and estrone to estradiol (KERSHAW & FLIER, 2004). In the testes, aromatase activity is found in Sertoli cells, before puberty, and in Leydig cells and testicular germ cells, including pachytene spermatocytes, elongated spermatids, and in

spermatozoa from the epididymis of adult male rodents (ABNEY, 1999; CARREAU et al., 2008; JOSEPH et al., 2011; SCHULSTER et al., 2016). Therefore, because obesity increases the amount of white adipose tissue, and consequently elevates levels of the aromatase enzyme, high estrogen concentrations may result from increased conversion of androgens to estrogens (YUXIN et al., 2021).

The alteration of the balance between androgens and estrogens may cause reproductive disorders (MOHAMED-ALI et al., 1998; AHIMA & FLIER, 2000). Increased levels of estradiol can reduce the release of Kiss-1, interfering with the regulatory control of GnRH secretion, and consequently of Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH), leading to decreased testosterone levels (HAMMOUD et al, 2006; PASQUALI, 2006; FUI et al., 2014; KATIB, 2015; KELLY & JONES, 2015; GRASA et al., 2017; WOLFE & HUSSEIN, 2018).

Leptin receptors present in the testis are related to the regulation of the HHG axis, so that increased leptin levels decrease testosterone production by Leydig cells (WAKE et al., 2007; COHEN, 2008; BLOUIN et al., 2009; GOMBAR & RAMOS, 2017; MISCH & PUTHANVEETIL, 2022).

Although obesity alters hormone levels, direct effects on testicular morphophysiology and spermatogenesis also occur (KORT *et al.*, 2006; HAMMOUD et *al.*, 2008; DAVIDSON ET AL., 2015; LEISEGANG et al., 2021; QI et al., 2022). Atrophy of the seminiferous epithelium and changes in the integrity and increased permeability of the hematotesticular barrier were evidenced in mice fed a high-fat diet for 10 weeks (FAN *et al.*, 2015).

The accumulation of adipose tissue causes impairment of scrotal and testicular thermoregulatory mechanisms, impairing testosterone synthesis, spermatogenesis and sperm maturation, reducing sperm quality (PALMER et al., 2012). In most mammals, scrotal temperature is about 2 to 4°C below body temperature, and is necessary for spermatogenic and sperm maturation processes to occur properly. The impact of elevated scrotal temperature in rodents and humans leads to reduced sperm viability, morphology and motility and reduced testicular blood flow. Direct effects of scrotal heating on germ cells include altered DNA, RNA and protein synthesis, as well as protein denaturation and abnormal chromatin condensation. This DNA damage in both testicular and epididymal spermatozoa is related to the increased oxidative stress promoted by increased scrotal temperature, which in turn causes changes in oxygen levels, water and ion transport mechanisms, protein biosynthesis and secretion, and the structure of the epididymal epithelium (SEILER et al., 2000; BANKS et al., 2005). Testicles submitted to heat stress present germ cell apoptosis; those that survive may complete spermatogenesis and form spermatozoa with damaged DNA. In the epididymis, a reduction in DNA integrity occurs along with a reduction in sperm concentration, which can be attributed to the increased removal of damaged spermatozoa by the basal cells in the epididymal epithelium, which act as macrophages (YEUNG et al.,1994; SEILER et al., 2000).

Heat stress also decreases the activity of antioxidant enzymes and increases the activity of the NADPH oxidase enzyme, leading to disruption of mitochondrial homeostasis), and in ATP production in spermatozoa (FERRAMOSCA et al., 2016; DARBANDI et al., 2018).

The literature is also controversial as to the effect that male obesity has on sperm parameters such as sperm motility, concentration, and morphology. However, clinical and experimental studies have shown that overweight and obesity are associated with oligozoospermia, damage to DNA integrity, and increased oxidative stress, affecting sperm function and embryo quality (SPANÒ et al, 2000; TRISINI et al., 2004; HAMMOUD et al., 2006; KORT et al., 2006; QIN et al., 2007; KRIEGEL et al., 2009; CHAVARRO et al., 2010; DU PLESSIS et al., 2010; HOFNY et al., 2010; MACDONALD et al, 2010; BAKOS et al., 2011; TEERDS et al., 2011; TUNC et al., 2011; FARIELLO et al., 2012; LA VIGNERA et al., 2012; PALMER et al., 2012; SERMONDADE et al., 2013; SHUKLA et al., 2014; CHAMBERS & RICHARD, 2015; KATIB, 2015; KIESS et al, 2015; ALSHAHRANI et al., 2016; CUI et al., 2016; MUSHTAQ et al., 2018; RAMARAJU et al., 2018; CHEN et al., 2020; LEISEGANG et al., 2020; MANN et al., 2020; RAHALI et al., 2020; SALAS-HUETOS et al., 2020). High expression of semenogelin-1, clusterin and lactotransferrin proteins, which are part of the *Eppin* (*epididymal proteinase inhibitor*) protein complex of the sperm membrane, and which play functions related to the process of sperm capacitation and fertilization, control of sperm motility and acrosome reaction (KORT et al., 2006; CHAVARRO et al., 2010; TUNC et al., 2011; DUPONT et *al.*, 2013), was also evidenced.

Oxidative stress is highly correlated with a wide variety of inflammatory and metabolic disease states, including obesity (VINCENT & TAYLOR, 2006 ; JIA et al., 2018). Imbalance between the generation of reactive oxygen species (ROS) and the activity of antioxidant enzymes results in oxidation of sperm membranes, which are mainly composed of polyunsaturated fatty acids, loss of mitochondrial function (WANG *et al.*, 2003; FARIELLO *et al.*, 2012).

The obesity-induced increase in ROS production, particularly in the region near the epididymis, can directly affect sperm quality and male fertility, as sperm are more susceptible to oxidative damage during their transit through the epididymal duct (AITKEN et al., 2010; MCPHERSON et al., 2019).

Hyperglycemia, increased oxidative stress and changes in the antioxidant enzyme system caused by obesity may be involved in the changes in the protein profile in spermatozoa and the lipoprotein layer of sperm membranes (DE LAMIRANDE et al., 2001; WANG et al., 2007; KRIEGEL et al., 2009; MITRA et al., 2010; PAASCH et al., 2011).

Increased adipose tissue around the epididymis and testis may indirectly contribute to the development of hypogonadism through an elevation in the production of pro-inflammatory cytokines, such as TNFα, IL-6 and IL-1β, and adipokines, such as resistin adiponectin, ghrelin, quemerin, visfatin, which can inhibit the activity of steroidogenic enzymes, decrease the production of testosterone by Leydig cells, leading to an inhibitory effect on HHG and thus on spermatogenesis and sperm maturation. Furthermore,

in the long term, adipose tissue-derived hormones and paracrine factors can impair the proliferation and differentiation of immature Leydig cells (HALES, 1992; LI et al., 1997; HALES, 2002; HONG et al., 2004; CABLER et al., 2010; WAGNER et al., 2016 ; LEISEGANG et al., 2019).

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