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Review

Energy Homeostasis and Kisspeptin System, Roles of Exercise and Outcomes with a Focus on Male Reproductive Health

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Abstract

Background: Obesity is a multisystemic health problem causing chronic diseases like diabetes or cardiovascular diseases, but also reproductive dysfunctions like infertility in adults or altered puberty onset in children. Exercise is a recognized intervention to control or prevent energy imbalance, thus deeply contributing to metabolic health in physiological and pathological conditions. The kisspeptin system (KS), the main gatekeeper of reproduction and puberty onset in mammals, is also an upcoming "metabolic sensor", linking energy homeostasis to reproductive ability both centrally and peripherally. Objectives: This narrative review aims at summarizing recent evidence from animal models and human studies on the role of the KS in energy homeostasis, with a focus on the upcoming role of the KS as a metabolic sensor able to modulate the functionality of the hypothalamus–pituitary–gonad axis in males as an adaptive response to exercise. Methods: PubMed and Scopus search (date: 2015–2025; keywords: kisspeptin and metabolism, male reproduction or exercise; kisspeptin and doping). Results and Conclusions: This review article illustrates the crucial role of the KS in linking energy homeostasis and male reproduction at the central and peripheral levels, and modulation of the KS by exercise in physiological and pathological conditions. Due to the large amount of data from animal models, knowledge gaps occur in the analysis of the relationship among KS, energy homeostasis, male reproduction and exercise in humans, particularly in the case of overtraining. Lastly, kisspeptin inclusion in the doping list is also discussed.

Keywords: kisspeptin system; obesity; energy homeostasis; metabolic sensors; arcuate nucleus; male reproduction; exercise; doping; athletes

Academic Editors: Jacques J. Tremblay, Antonio Brunetti and Maria Mirabelli

Received: 20 May 2025
Revised: 20 August 2025
Accepted: 26 August 2025
Published: 28 August 2025

Citation: Ruggiero, M.; Vicidomini, A.; Tafuri, D.; Mazzeo, F.; Meccariello, R. Energy Homeostasis and Kisspeptin System, Roles of Exercise and Outcomes with a Focus on Male Reproductive Health. *Endocrines* **2025**, *6*, 43. https://doi.org/10.3390/endocrines6030043

1. Introduction

Over-consumption of calorie-rich foods and a sedentary lifestyle are the main causes of energy imbalance, overweight, and obesity. Obesity is a multisystemic health trouble causing several chronic diseases like diabetes, cardiovascular diseases, metabolic syndrome, and also reproductive-related diseases like infertility [1]. According to the World Health Organization (WHO), in 2019, an estimated 5 million non-communicable disease (NCD)

deaths were caused by higher-than-optimal body mass index (BMI) [2]. Hence, the global burden of obesity constitutes a major public health challenge that undermines social and economic development throughout the world. Key points for any weight loss effort are lifestyle habits, diet and physical activity; in this respect, the WHO recommends engaging in regular physical activity to prevent and manage overweight and obesity [2].

At the molecular level, the control of energy homeostasis involves several peripherally produced signaling molecules acting both at the central and peripheral levels. Such molecules include: (1) leptin (Lep), produced by the adipose tissue and suppressing feeding; (2) ghrelin, produced by the gut and inducing food intake; (3) peptides from the gut suppressing food intake (glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), vasoactive intestinal peptide (VIP), insulin); (4) hypothalamic arcuate nucleus (ARC) orexigenic peptides (Neuropeptide Y (NPY), melanin-concentrating hormone (MCH), agouti-related protein (AgRP)); (5) ARC anorexigenic peptides (proopiomelanocortin (POMC), cocaine and amphetamine regulated transcript (CART), α melanocyte stimulating hormone (α-MSH) [3,4]. Some relevant pathways involved in appetite are summarized in Figure 1.

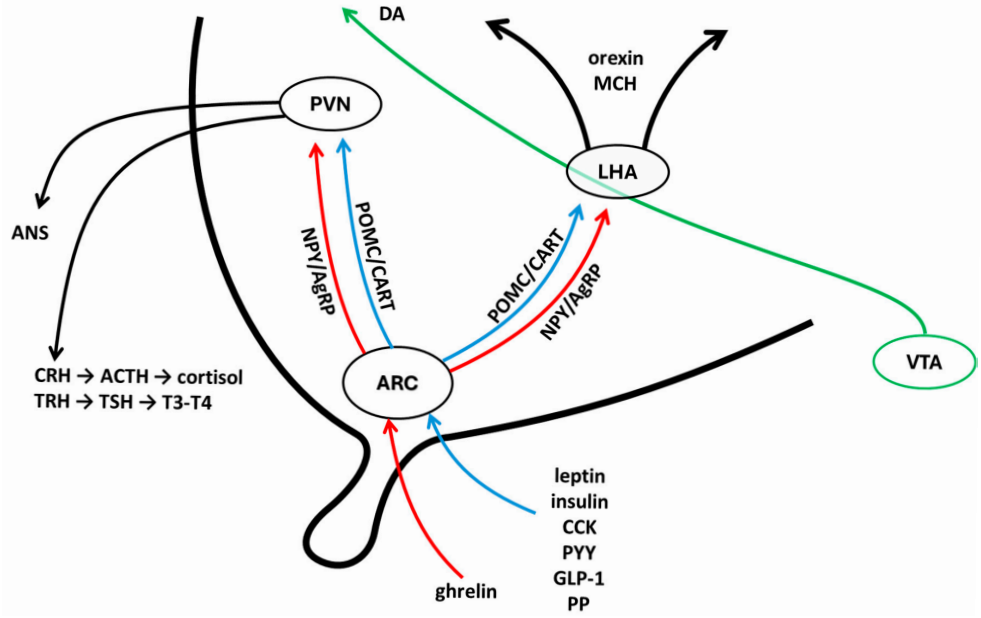

Figure 1. Some relevant pathways involved in appetite. The arcuate nucleus (ARC) is responsive to many plasma peptides correlated with increased (red arrow) or reduced food intake (blue arrow). Different ARC neurons release different neuropeptides regulating paraventricular (PVN) and lateral hypothalamic area (LHA) activity correlated with increased (red arrow) or reduced (blue arrow) food intake. PVN neurons can regulate the metabolic rate due to a direct connection with autonomic neurons and the release of CRH and TRH. LHA neurons project widely within the brain and release melanin-concentrating hormone (supposed to promote food intake) and orexin (an important regulator of the sleep/awake state). LHA is also on the way of dopamine (DA) neurons projecting from the ventral tegmental area (VTA) to the forebrain; DA neurons are responsible for the effect of reinforcing stimuli, including the reinforcement produced by feeding. ACTH, adrenocorticotropic hormone; AgRP, Agouti-related peptide; ANS, autonomic nervous system; ARC, arcuate nucleus; CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; CRH, corticotropin releasing hormone; DA, dopamine; GLP-1, glucagon-like peptide-1; LHA, lateral hypothalamic area; MCH, melanin-concentrating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY; PVN, para-ventricular nucleus; T3, triiodothyronine; T4, tetraiodothyronine; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone; VTA, ventral tegmental area.

Since sex maturation and reproduction require a minimum threshold of energy reserves, the orexigenic and anorexigenic signals in the ARC are strictly related also to neuronal circuitry critical for reproduction, including, in particular, gonadotropin-releasing hormone (GnRH)-secreting neurons that release the decapeptide GnRH in the portal vessels to reach pituitary gland, which, in turn, discharge gonadotropins (i.e., follicle stimulating hormone (FSH) and luteinizing hormone (LH)), to sustain sex steroid production and gametogenesis [4,5]. Consistently, the ablation of Lep signaling in animal models causes both infertility and obesity [6–8]. Thus, Lep adapts the functionality of the hypothalamus–pituitary–gonad (HPG) axis to energy availability through the modulation of orexigenic/anorexigenic neurons in the ARC, and also affects glucose metabolism in the liver [9,10].

Indeed, the strict links between energy homeostasis and reproduction are confirmed in humans, since obesity has been related to precocious puberty and polycystic ovary syndrome in children and adolescents, while low levels of estradiol in menopausal women and low testosterone levels in men have been correlated to body weight gain [11–14].

In recent years, the Kisspeptin System (KS), which includes the cleavage products of the KISS1 pre-pro-hormone (i.e., Kp10, 13, 14, 15) encoded by the *KISS1* gene and the kisspeptin receptor (Kiss1R, previously known as GPR54), entered the neuronal crosstalk between metabolic cues and reproduction [15]. Currently, the KS represents not only the well-recognized gatekeeper of the HPG axis, particularly at puberty [15], but also an upcoming "metabolic sensor", linking energy homeostasis to reproductive ability both centrally and peripherally [16,17].

Exercise is a recognized and effective intervention to control and prevent energy imbalance, thus deeply contributing to the control of energy homeostasis and metabolic health in physiological and pathological conditions at any age [2]. The beneficial effects of an active lifestyle and exercise are well recognized, but several knowledge gaps occur in the analysis of the relationship between energy homeostasis, reproduction and exercise, particularly in the case of overtraining. In addition, the possible role of the KS as an intermediate in the adaptive response to environmental factors like exercise is poorly understood in humans, but evidence from animal models is corroborating this correlation.

This narrative review summarizes the main evidence derived from animal models and studies in humans (pre-clinical and clinical studies) on the correlation between energy homeostasis and the KS, both centrally and peripherally. The role of exercise and the outcomes on male reproduction are also discussed in animal models and humans, providing evidence about the emerging role of the KS as a metabolic sensor able to modulate the functionality of the HPG axis in response to exercise. The recent inclusion of kisspeptin and its analogues in the World Anti-Doping Agency (WADA) Prohibited List is also discussed.

Methods

A PubMed and Scopus search was carried out, and research articles published between 2015–2025 reporting studies in cells, animal models (i.e., mouse and rat) and humans were considered. Keyword searches incorporated the following terms: "kisspeptin and metabolism", "kisspeptin and metabolism and male reproduction or exercise", and "kisspeptin and doping". The scientific background was further developed through analysis of master review articles identified by the search terms: "obesity and energy homeostasis", "HPG axis and male reproduction", "kisspeptin", and "athlete performance and doping".

2. Energy Homeostasis, KS and Reproduction at the Central Level

Originally, the *KISS1* gene has been functionally related to the suppression of metastasis [18]; nevertheless, the widespread distribution of the Kiss1R and data from knockout

animals undoubtedly linked the KS to reproduction [15]. In mammals, the KS is recognized as the "gatekeeper of reproduction" due to its ability to induce gonadotropin secretion through the stimulation of hypothalamic GnRH-secreting neurons [15]. Consistently, loss-of-function mutations in the *KISS1* or *KISS1R* genes cause hypogonadotropic hypogonadism in humans [19–22], whereas activating mutations in the *KISS1R* causes precocious puberty [23]. Within the hypothalamus, Kiss1-secreting neurons (Kiss1 neurons) are localized in the ARC and are also referred to as KNDy neurons, due to their ability to co-express Kiss1, the tachykinin neurokinin B and the endogenous opioid dynorphin A. They are capable of inducing GnRH pulsatile secretion and gonadotropin discharge in turn. Specifically, KNDy neurons modulate GnRH secretion, since kisspeptin directly stimulates GnRH secretion, while dynorphin A and neurokinin B, respectively, inhibit and induce Kiss1 [24,25]. In the hypothalamus of females, Kiss1 neurons are also located within the anteroventral periventricular nucleus/periventricular nucleus continuum (AVPN/PeN) and are specifically related to the positive feedback loop exerted by ovarian estradiol on GnRH-secreting neurons to induce ovulation [15].

The hypothalamic Kiss1 neurons represent the main conveyor of environmental cues and lifestyle like stressors, energy homeostasis, diet or sedentary life to control the functionality of the reproductive axis, thus affecting the timing of puberty onset and reproductive functions. The metabolic status affects the hypothalamic expression of the *Kiss1* gene, with decreased levels of *Kiss1* mRNA observed in the ARC of obese female mice [26], fasted rodents [27,28], or in diabetic male rats [29]. Interestingly, KNDy neurons within the ARC co-express insulin receptor and Lep receptor and may function as an intermediate in the communication between the ARC orexigenic and anorexigenic neurons and the GnRH-secreting neurons [4,16,17], thus linking energy balance to reproduction. For example, within the ARC, the feeding-inducing signals AgRP and NPY directly inhibit Kiss1 neurons under energy-deficient conditions. Consistently, obesity alters the crosstalk between POMC and Kissp1 neurons, reducing LH in male mice [30,31]. This crosstalk is reciprocal since the kisspeptin antagonist KP234 regulates POMC neurons and also NPY neurons through an indirect mechanism based on enhancing the GABA-mediated inhibitory synaptic tone [30].

Both AgRP neurons and Kiss1 neurons respond to Lep that is secreted by adipocytes into the bloodstream with a direct correlation with fat reserves [32–36]. Interestingly, infertility and obesity occur in animal models deficient in Lep signaling (i.e., ob/ob *or* db/db mice) [6–8].

Lastly, Kiss1 neurons in the ARC also participate in the modulation of circadian rhythms, specifically those concerning food intake and metabolism [37]. In fact, the i.c.v. injection of kisspeptin reduces food intake [38–40], while in *Kiss1R* Knockout, obesity develops [41]. Conditional knockout within the Kiss1 neurons in the ARC also produces body weight gain [42], but the selective reactivation of *Kiss1R* in the GnRH neurons restores all the metabolic features observed in knockout animals. Interestingly, this occurs only in males and not in females, thus revealing sexually dimorphic mechanisms possibly involving sex steroid-mediated pathways [43].

Taking also into consideration the upcoming roles of the KS in the circadian control of feeding behavior [37], the KS may act in the ARC as a neuroendocrine player in energy expenditure rather than in food intake [17]. To date, melatonin, the methoxyindole synthesized and secreted principally by the pineal gland at night under normal light/dark conditions that regulates the rhythmicity of physiological functions, is a modulator of kisspeptin release and puberty timing [44–46]. Consistently, melatonin treatment suppresses the expressions of *Kiss1, Kiss1R* and *GnRH* in the hypothalamus, and the expression of *GnRHR* in the pituitary of female mouse model of central precocious puberty [47].

Changes in the hypothalamic KS due to energy homeostasis may be reversible, and epigenetic mechanisms involving DNA methylation, histone tail modifications, and the production of non-coding RNA have been reported and elsewhere reviewed [17,48,49]. Hence, the molecular, cellular, endocrine and neuroendocrine modulation of KS allows Kiss1 neurons to respond to circulating factors like Lep or ghrelin, adapting reproduction to energy state.

Particularly studied is the involvement of KS as a determinant for puberty onset in mammals. Since 1971, when Frisch and Revelle proposed the "critical body weight hypothesis" for the determination of puberty onset [50], increasing evidence confirms that this critical process is largely dependent on body weight rather than chronological age in several mammalian species and in humans [51].

In rat models, undernutrition can delay puberty onset in females through the suppression of *Kiss1* and *dynorphin A* (*Pdyn*) expression in the ARC, whereas ad libitum feeding increases the number of *Kiss1* and *Pdyn*-expressing neurons in the ARC, and *Kiss1* in the AVPV, thus stimulating the secretion of LH and inducing puberty onset in the growth-retarded female rats [52]. The metabolic sensor SIRT1, a NAD^+ dependent deacetylase capable of epigenetically modulating gene expression [53,54], restrains female puberty via epigenetic repression of *Kiss1* transcription through the interaction with the polycomb silencing complex to decrease the activity of the *Kiss1* promoter [49]. Overnutrition anticipates the eviction of SIRT1 from the *Kiss1* promoter, thus leading to early puberty onset; consistently, undernutrition delays *Kiss1* expression, retaining the *Kiss1* promoter in a repressive state [49]. Hence, data in mammalian animal models revealed the need for suitable energy availability to switch chromatin landscape into a permissive status to favor the transcription of the *Kiss1* gene, meaning that nutritional cues and obesity affect female puberty in mammals via SIRT1.

Recently, male puberty was also investigated [55]. Several binding sites for the transcription factor Nescient Helix-Loop-Helix 2 (encoded by the *Nhlh2* gene) have been identified in the 5′regulatory regions of *Kiss1* and *Tac3*, the latter encoding for neurokinin B in humans. Consistently, conditional knockout of *Nhlh2* in the Kiss1 neurons of the ARC delays the onset of puberty in male mice, but not in females. Lastly, impaired response to Lep and a higher susceptibility to metabolic changes in LH secretion have also been suggested in the absence of *Nhlh2* in Kiss1 neurons [55].

3. Energy Homeostasis, KS and Reproduction at Periphery

Beyond the hypothalamus, in vertebrates, the KS has been characterized in different brain areas [51,56] and at the periphery in male gonads and gametes [57], liver, pancreas and white and brown adipose tissue (WAT and BAT, respectively) [16].

In the testis of vertebrates, the distribution of Kiss1/Kiss1R revealed species-specific patterns [57–59], but, in general, the activity of the KS has been linked to the modulation of gene expression and steroidogenesis in Leydig cells [57,60–62], and spermatogenesis progression within the germinal epithelium, as reviewed elsewhere [57]. A significant crosstalk has been characterized between the estrogen and the endocannabinoid systems [63–67], two major signaling systems notably involved in the physiology of the testis and the production of high-quality gametes [51,57,68], and also in metabolism, energy homeostasis and obesity [4,69,70].

The production of high-quality gametes is affected by lifestyle and nutritional status, as obesity can affect male fertility with a negative impact on the reproductive axis and on semen quality; the possibility of transferring to offspring an impaired epigenetic signature also occurs [71,72].

Apart from reproductive impairment, data from knockout/conditional-knockout revealed that the lack of KS signaling causes obesity and diabetes [37] as a consequence of the impairment of KS signaling within the pancreas and the BAT, in which the KS is functional for glucose tolerance and energy expenditure. Hence, accumulating data from animal models suggest that, besides reproduction, the KS signaling regulates several metabolic parameters, including body weight, energy expenditure, food intake, glucose metabolism, adipose tissue function and deposition, respiratory rates, locomotor activity, and thermoregulation, as recently reviewed [37,56].

The relationship between circulating hormones and metabolic status has been investigated in clinical studies. To date, low testosterone levels in men cause body weight gain [14]. Accordingly, a multicenter study, carried out on a cohort of n.3369 European men demonstrated that obesity severity correlates with the effects on male reproduction. In fact, a BMI of 30 kg/m^2 or higher has been associated with secondary hypogonadism (i.e., low testosterone and low/normal LH) [73]. Also, circulating kisspeptin levels negatively correlate with BMI in humans and have been associated with the secretion of insulin in non-diabetic subjects [74]. Lastly, a cross-sectional, observational study reported lower circulating kisspeptin and primary hypogonadism in men with type 2 diabetes [75]. A recent manuscript by Izzi-Engbeaya et al. investigated the effects of kisspeptin during intravenous glucose challenges on β-cell function, serum metabolites and appetite in 15 healthy men (mean BMI: 22.3 $\pm$ 0.5), revealing, for the first time, a beneficial role of kisspeptin on insulin secretion in humans in vivo [76]. This finding may be useful for the ongoing development of kisspeptin-based therapies for both reproductive and metabolic conditions. Nevertheless, there is a need for further clinical studies in the field to fill several knowledge gaps in the relationship between circulating levels of kisspeptin, energy homeostasis and related metabolic diseases.

4. Energy Homeostasis, KS and Exercise: The Outcomes on Reproduction

The combination of a healthy diet and physical exercise is the most effective approach to achieve significant weight loss in the management of obesity [77]. Table 1 summarizes the WHO physical activity guidelines, categorized by population group, and includes examples of recommended exercises. Hence, physical exercise is a recognized "therapeutic approach" in the treatment of obesity due to its pleotropic effects on muscle, liver, bone, neuroendocrine and cardiovascular systems. As a consequence, via the production of exercise-inducible soluble factors (e.g., myokines, adipokines, hepatokines, osteokines, or cytokines among the others), it has a role in the loss of body fat mass, in optimizing global energy expenditure with redistribution of energy substrates, in decreasing systemic inflammation, in improving glucose uptake, and in enhancing hypothalamic circuits that control appetite-satiety circuitry [78].

Table 1. Physical activity guidelines by population group: recommendations and adaptable examples.

Population Group	Recommended Physical Activity	Examples of Activities	Notes
Children and Adolescents (5–17 years)	At least 60 min/day of moderate-to-vigorous physical activity, mostly aerobic. 3 days/week: vigorous activity + muscle- and bone-strengthening exercises.	Active play, running, swimming, cycling, team sports (soccer, volleyball) [79,80]	Limit sedentary time, especially screen time.
Adults (18–64 years)	150–300 min/week of moderate aerobic activity or 75–150 min/week of vigorous activity. 2 days/week: muscle-strengthening exercises.	Brisk walking, swimming, running, intense cycling [81,82]	Replace sedentary time with activity of any intensity.
Older Adults (65+ years)	150–300 min/week of moderate aerobic activity or 75–150 min of vigorous activity. 2 days/week: muscle-strengthening. 3 days/week: balance exercises (e.g., multicomponent).	Walking, pilates, dancing, gardening, light weight exercises, fall-prevention exercises [83,84]	Adapt intensity to physical abilities.
Pregnant and Postpartum Women	150 min/week of moderate aerobic activity. Muscle-strengthening and stretching exercises. May continue vigorous activity if already habitual.	Walking, swimming, prenatal yoga, pelvic floor exercises [85–87]	Avoid high-risk activities (falling/overexertion). Consult a doctor.
People with Disabilities	Same recommendations as their age group, adapted to individual abilities. Consult a specialist for personalized activities.	Adapted sports (e.g., wheelchair basketball, mixed ability rugby), water exercises, stretching [88,89]	Ensure inclusive and safe opportunities.
People with Chronic Conditions (e.g., diabetes, hypertension, cancer)	Same recommendations as adults/older adults, adjusted for health conditions. Consult a doctor to plan activities.	Walking, swimming, cycling, light resistance exercises [90–92]	Physical activity improves disease management.

Data from Ref. [93].

In addition to Lep, adipose tissue also produces adiponectin, an adipokine with a recognized role in insulin resistance, diabetes, and the metabolic syndrome because of its antidiabetic and antiatherogenic effects, due to antioxidant and antinflammatory activities [94]. Circulating adiponectin levels are decreased under obesity conditions in both animal models and clinical studies [94], and are increased following exercise [95]. In this respect, adiponectin from skeletal muscle may function as a myokine that acts in an autocrine/paracrine manner to protect muscle from environmental insults like a high-fat diet; nevertheless, when metabolic insults are sustained or obesity occurs, the expression of muscle adiponectin decreases and this protective response fails [96]. Nevertheless, adiponectin also contributes to the inhibition of *Kiss1* expression in different contexts, like primary culture of rat islets of Langerhans and CRI-D2 cell line [97], hypothalamic GT1-1 neurons [98] or ovary [99].

The adipose tissue is both a source and a target for kisspeptin since its ability to expresses both ligand and receptor, thus responding to locally or distantly produced kisspeptin. In fact, exercise increases the expression of the *Kiss1* gene just within the adipose tissue, as a consequence of exercise-induced adaptive responses, as demonstrated in genetically modified animal models (i.e., adipose-specific *Kiss1* knockout and adipose tissue *Kiss1*-overexpressing mice) [100]. In particular, after prolonged aerobic exercise, the effects of the adipose-derived kisspeptin signal on glucose and lipid homeostasis in gonadal WAT and the expression of metabolic related cofactors in soleus muscle (i.e., Peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α) and maximum oxygen uptake

(VO_{2max})) were more significant in females than male mice, suggesting that kisspeptin acts as an adipokine that, in a sex-specific manner, increases organ sensitivity to glucose, lipids, and oxygen consumption following aerobic exercise [100].

Nevertheless, in spite of the efficacy of aerobic exercise in improving several undesirable health outcomes, its implications in the HPG axis are still controversial, at least in males. We summarize in the next section the main evidence in animal models and humans.

4.1. Animal Models

In this respect, recent studies in animal models reported the modulation of the KS in the exercise-induced modulation of reproduction, once again confirming the strong link between energy homeostasis, male HPG axis and exercise. In male rats, forced and prolonged swimming exercises exerted negative effects on the HPG axis, reducing *Kiss1, Kiss1R, GnRH* mRNA within the hypothalamus, *GnRH Receptor* (*GnRHR*) mRNA in pituitary, *Kiss1R* mRNA in testis, and decreasing serum levels of both gonadotropins (LH and FSH) and testosterone, with negative impact on gametogenesis and sperm production and quality, probably due to increased oxidative stress and reduced oxidative stress defenses [101]. Conversely, exercise ameliorates the impairment of the male HPG axis in the case of energy imbalance with mechanisms involving the kisspeptin-GnRH neuronal networks. The effects of aerobic exercise (i.e., treadmill running) on the KS have been recently reported under different experimental conditions. Exercise carried out from early childhood (post natal day, PND 21) to puberty onset (PND 43) and sex maturity (PND 56) was able to correct the adverse effects of HFD on the physiological expression of the hypothalamic KS during post-natal development, ensuring the functionality of the male HPG axis and the activity of Leydig cells in testosterone biosynthesis [102]. In obesity induced adult rats, exercise improves the sexual behavior disorder dependent on HFD and increases the expression of *Kiss1*/*Kiss1*R in brain areas associated with reproduction and sexual behavior (i.e., prefrontal cortex, hypothalamus, hippocampus and corpus striatum) [103]. Curiously, exercise alone significantly decreased the expression rate of both *Kiss1* and *Kiss1*R within the aforementioned brain areas [103], in agreement with the reports by Arisha et al., showing a reduction in Kiss1 and Kiss1R expression within the hypothalamus and a consequent reduction in testosterone levels, following forced swimming in normo-weight male rats [101]. Chang et al. observed increasing levels of tumor necrosis factor alpha (TNF-α) and decreased levels of GnRH, LepR, *Kiss1* (but not *Kiss1*R), and anti-inflammatory interleukin-10 (IL-10) at mRNA and protein levels within the hypothalamus of HFD-induced obese mice; in parallel, poor sperm quality (i.e., low sperm count, low sperm motility and high sperm apoptosis rate), low gonadotropins (both LH and FSH) and testosterone, high circulating estradiol, leptin and TNF-α were detected in the serum of obese mice [104].

Obesity and metabolic dysfunction may often be attributed to a difficulty for Lep to cross the blood–brain barrier and/or interact with its own receptor. This condition is known as Lep resistance and is characterized by reduced satiety, over-consumption of nutrients, and increased total body mass [105]. Interestingly, both moderate and high load exercise reduced Lep levels and body fat, but the intensity of the aerobic exercise produced different effects on the HPG axis of obese male mice. In fact, while high load exercise promoted inflammation without any beneficial effect on the hypothalamic Kiss1/GnRH, testosterone production and sperm quality, moderate load exercise produced anti-inflammatory effects, improved Lep resistance, and in parallel ameliorated gonadotropin discharge and testosterone biosynthesis via the increased expression of *Kiss1* and *GnRH* [82]. Hence, in conditions of energy imbalance and high load exercise, Lep and inflammation have a synergic effect on the negative regulation of the male HPG axis through the modulation of

hypothalamic *Kiss1*. Consistently, eccentric exercise leads to hypothalamic inflammation, with concomitant reduction in food intake and body weight gain in overtrained mice; however, after 2 weeks of recovery, the effects on neuroinflammation, food intake and body weight were totally reversed [106].

In a study by Khajehnasiri et al. [107], the effects of a prolonged moderate or intensive exercise on the male HPG axis were compared, revealing that intensive exercise only decreased *GnRH* mRNA and circulating testosterone; both training protocols increased *Pdyn* mRNA levels in the ARC, whereas prolonged moderate exercise only decreased *neurokinin B* (*Nkb*) mRNA. Hence, a different modulation of the KNDy neurons by exercise intensity may cause different outcomes on the HPG axis. Consistently, in mice, a high-fat diet causes obesity and a decline in sperm quality via leptin resistance and an impairment of the testosterone/estradiol ratio via the Lep–JAK–STAT pathway. Both moderate and high-volume exercises were able to reduce body fat, but moderate exercise only rescued sperm quality and the sex steroids ratio [108].

4.2. Studies in Humans

Besides animal models, studies in humans are poor and the data are almost contradictory. A short-term intervention program based on aerobic training, i.e., a 16-week aerobic training program on a treadmill, improved semen quality in sedentary obese adults (n = 45 obese vs. n = 45 controls). This finding may be explained, at least in part, by an improvement in the reproductive hormone profile [109] with an increase in serum testosterone. The same study reported significant correlations between seminal outcomes and abdominal obesity [109]. Data from the Longitudinal Investigation of Fertility and the Environment (LIFE) study revealed that in a cohort of n = 501 couples attempting to conceive, the percentage of men with abnormal volume, concentration and total sperm increased with increasing body size, but the authors did not identify any relationship between physical activity and semen parameters [110]. In a trial by Rafiee et al., semen parameters and BMI ameliorated after six months of exercise intervention [111]. Lastly, a prospective study by Wise et al. investigated the association between cycling and fertility in men from two cohorts, from Denmark and North America, revealing that, in general, the average hours/week of vigorous physical activity, moderate physical activity and total metabolic equivalents were inversely associated with fecundability in the European cohort only; the authors also warrant the need for further evaluations in the field taking into consideration also BMI and the possible effect of bike seat type [112].

Since the role of sex hormones in muscle development, bone density, or energy homeostasis [113], and the ability of the KS to modulate the functionality of the HPG axis and sex steroid production [57], the link between the KS, energy availability and reproductive function deserves attention in sport. Nevertheless, the situation in athletes is quite controversial due to the paucity of focused studies in the field. Table 2 summarizes the connections between the KS, energy availability, reproductive function, and potentially bone health in athletes.

Table 2. KS and its connection between energy availability, reproductive function, and potentially bone health in athletes.

	Description	Implications for Sport
Primary Role	Central regulation of the hypothalamic–pituitary–gonadal (HPG) axis, which controls reproduction through the release of *GnRH* (Gonadotropin-Releasing Hormone).	Influences the production of sex hormones (testosterone in men, estrogen in women), important for muscle development, bone density, energy, and libido, all relevant factors for athletic performance [113]. GnRH: Section S2 of the World Anti-Doping Agency (WADA) Prohibited List [114].
Response to Exercise	Physical exercise can influence kisspeptin levels. The response may vary depending on the intensity, duration, and type of exercise, as well as the individual's energy status.	Intense and/or chronic exercise, especially in combination with caloric restriction (common in some sports), can suppress the kisspeptin system, leading to a reduction in sex hormones [113]. This can have negative consequences on performance, recovery, and general health (e.g., bone density, menstrual cycle in women) [115].
Energy Balance	The kisspeptin system is sensitive to energy status. Low energy levels (caloric deficit) can inhibit the activity of kisspeptin neurons.	Athletes in sports that require low body weight or who follow restrictive diets are at risk of overthrow of the kisspeptin system, with potential negative impacts on reproduction and metabolic health [116].
Gender Differences	There are differences in the regulation of the kisspeptin system between men and women, as well as in the response to exercise.	Female athletes may be more susceptible to exercise-induced hormonal imbalances due to the complex interaction between the kisspeptin system, the menstrual cycle, and energy balance [117].
Potential Applications	Understanding the role of kisspeptin in sport could lead to strategies to optimize hormonal health and athletic performance; for example, through targeted nutritional or training interventions.	Monitoring kisspeptin and related hormone levels could be useful in identifying athletes at risk of hormonal imbalances. Interventions to maintain adequate energy balance and modulate training intensity could preserve the function of the kisspeptin system and hormonal health [118,119].

In fact, the suppression of the HPG axis can occur in the context of energy deprivation by caloric restriction, especially in combination with excessive energy expenditure. This condition has been largely described in female athletes as the "female athletic triad" consisting of disordered eating, amenorrhea and osteoporosis [120]. However, the relationship between overtraining, energy homeostasis and neuroendocrine/reproductive axis has been poorly described in male athletes and is quite limited to muscle dysmorphia, a condition that overlaps with anorexia and eating disorders [121]. Nevertheless, in 2014, the International Olympic Committee (IOC) defined "Relative energy deficit in sport (REDS)" as the condition of whole body energy deficits due to inadequate caloric intake in the context of excessive exercise (overtraining) [122]. During states of energy deficit, such as starvation or intense exercise without adequate caloric intake, the levels of metabolic signals like leptin decrease [119]. This can lead to a reduction in kisspeptin secretion, subsequently suppressing the GnRH–LH/FSH axis and potentially impairing male reproductive function. This is a protective mechanism to save energy when resources are scarce [104]. The impact of exercise on the KS and male reproduction is complex and depends on the intensity, duration, and type of exercise, as well as the individual's energy balance. Prolonged, high-intensity exercise, especially when coupled with insufficient energy intake, can lead to a state of negative energy balance [123]. This can result in decreased kisspeptin levels and subsequent suppression of the HPG axis, potentially leading to reduced testosterone levels and impaired spermatogenesis. Studies in animal models have shown that chronic intense exercise can downregulate the expression of kisspeptin and GnRH signaling components. Moreover, some studies suggest that moderate regular exercise might have a beneficial impact on the male reproductive axis [124].

Is There a Link Between the KS and Doping?

KS's role in stimulating the release of gonadotropins, which in turn boost testosterone production, has led to concerns about its potential misuse as a doping agent in sports [125]. By increasing LH and FSH levels, kisspeptin and its agonists can elevate testosterone production, particularly in males. Testosterone is a well-known anabolic steroid that increases muscle mass, strength, and recovery, providing a potential advantage in athletic performance (doping) [126,127]. In addition to testosterone, kisspeptin can stimulate the production of the growth hormone (GH), although the stimulatory effects are variable according to context and species [128–130]. Identifying this potential for misuse, the WADA has explicitly added "kisspeptin and its agonist analogues" to the list of prohibited substances, either in-competition and out-of-competition. They are classified under "S2. Peptide Hormones, Growth Factors, Related Substances, and Mimetics, specifically within the subcategory of S2.2.1 Testosterone-Stimulating Peptides in Males". Therefore, kisspeptin agonists represent a form of "indirect androgen doping." Instead of directly administering testosterone or other anabolic steroids, they stimulate the body's own production of testosterone. Nevertheless, anti-doping agencies are actively involved in research to develop effective detection methods, often through sophisticated techniques like liquid chromatography-high-resolution mass spectrometry (LC-HRMS). An important contest is differentiating naturally occurring kisspeptin from synthetic peptides and establishing reference ranges for endogenous kisspeptin levels [90]. Studies are ongoing to understand the metabolism of kisspeptin and its analogues to identify specific metabolites that can serve as markers for doping [114,131].

In conclusion, the KS plays a crucial role in naturally boosting testosterone levels by stimulating the release of LH and FSH from the pituitary gland. These hormones then act on the testes to increase testosterone production. While the KS is a natural regulator of testosterone, its potential for misuse as a performance-enhancing substance has led to its prohibition by WADA. Ongoing scientific efforts are crucial to developing effective detection strategies to maintain the integrity of sports.

5. Conclusions

The KS plays a crucial role in regulating reproductive function in both sexes. Recently, the role of kisspeptin in linking energy homeostasis to reproduction in the brain and at the periphery as an adipokine has emerged. This intricate interplay means that the body's energy status significantly influences male reproductive competencies [132]. It is well-known that the KS acts as a central modulator of the HPG axis, thus affecting the endocrine route (i.e., GnRH, gonadotropins and sex steroids), which is essential for spermatogenesis [5,53,54] and the development of male secondary sexual characteristics [133]; nevertheless, in the hypothalamic ARC, Kiss1 neurones convey on the reproductive axis orexigenic and anorexigenic signals to adapt reproduction to energy availability [16]. Beyond the brain, studies in animal models or cell lines revealed that the KS is an intratesticular modulator of spermatogenesis and sex steroid biosynthesis [62–67], but also a metabolic sensor related to the physiology of liver, adipose tissue or pancreas [16]. Consistently, circulating kisspeptin levels are higher in fertile men compared to infertile men, further underlining its importance in male reproductive health [72,75,134], and negatively correlate with BMI [74].

Physical exercise is a key modulator of energy balance and a recognized therapeutic intervention in the treatment of obesity. Upcoming evidence from animal models has revealed that physical exercise can also exert considerable effects on the KS, adapting the functionality of the HPG axis to environmental cues. In fact, exercise can affect the expression of the hypothalamic KS and, consequently, the production of sex steroids and male

reproduction, with effects mainly depending on the intensity of the training programme. For example, chronic, strenuous exercise, such as prolonged swimming, suppressed the kisspeptin-*GnRH* signaling pathway, leading to decreased levels of reproductive hormones and impaired sperm parameters. On the contrary, moderate physical activity may have beneficial effects on general health and potentially reproductive function [135]. This suggests that the intensity and duration of exercise can influence the male reproductive axis through the KS [101]. Unfortunately, the link between exercise, KS and male reproduction is poorly studied in humans, and the few available data on exercise and male reproduction are almost contradictory, with either no correlation or some beneficial effects on male reproduction after exercise intervention or training, particularly in the case of overweight or obesity [86–89].

Hence, a full understanding of the role of this system is essential to develop strategies to preserve male reproductive health under different physiological conditions and in response to various lifestyles, including physical activity. Further research is needed to delineate the precise mechanisms by which exercise influences the KS and the long-term consequences for male fertility.

KS has the ability to modulate the functionality of the HPG axis and sex steroid production as a consequence [57]; sex steroids affect the physiology of muscle, bones, adipose tissue, and energy homeostasis in turn [113]. Hence, the link between the KS, energy availability and reproductive function deserves attention in sport. Currently, the situation in athletes is quite controversial due to the paucity of focused studies in the field. Nevertheless, kisspeptin and its agonist analogues were added to the WADA Prohibited List in 2024 as a substance with a high potential for misuse in sports doping [136]. Ongoing research by anti-doping agencies is focused on developing detection methods to prevent its illicit use and ensure fair competition [131,137]. Athletes should be aware of the potential health risks and ethical implications associated with using such investigational substances. Nevertheless, the suppression of the HPG axis via KS reported in animal models after intensive training deserves interest in athletes. In this respect, the relationship between overtraining, energy homeostasis and the neuroendocrine/reproductive axis has been poorly described in male athletes, and there is a need to fill this knowledge gap.

Author Contributions: Conceptualization, F.M. and R.M.; writing—original draft preparation, M.R., A.V., F.M. and R.M.; writing—review and editing, D.T., F.M. and R.M.; supervision, R.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. WHO Infertility. Available online: https://www.who.int/news-room/fact-sheets/detail/infertility (accessed on 15 July 2025).
2. WHO Obesity. Available online: https://www.who.int/health-topics/obesity/#tab=tab_1 (accessed on 15 July 2025).
3. Valassi, E.; Scacchi, M.; Cavagnini, F. Neuroendocrine Control of Food Intake. *Nutr. Metab. Cardiovasc. Dis.* **2008**, *18*, 158–168. [CrossRef]
4. Chianese, R.; Coccurello, R.; Viggiano, A.; Scafuro, M.; Fiore, M.; Coppola, G.; Operto, F.F.; Fasano, S.; Laye, S.; Pierantoni, R.; et al. Impact of Dietary Fats on Brain Functions. *Curr. Neuropharmacol.* **2018**, *16*, 1059–1085. [CrossRef]
5. Kaprara, A.; Huhtaniemi, I.T. The hypothalamus-pituitary-gonad axis: Tales of mice and men. *Metabolism* **2018**, *86*, 3–17. [CrossRef]

6. Donato, J.J.; Cravo, R.M.; Frazão, R.; Elias, C.F. Hypothalamic Sites of Leptin Action Linking Metabolism and Reproduction. *Neuroendocrinology* **2011**, *93*, 9–18. [CrossRef]
7. Leshan, R.L.; Björnholm, M.; Münzberg, H.; Myers, M.G. Leptin Receptor Signaling and Action in the Central Nervous System. *Obesity* **2006**, *14* (Suppl. S5), 208S–212S. [CrossRef]
8. Navarro, V.M.; Kaiser, U.B. Metabolic Influences on Neuroendocrine Regulation of Reproduction. *Curr. Opin. Endocrinol. Diabetes Obes.* **2013**, *20*, 335–341. [CrossRef]
9. Evans, M.C.; Campbell, R.E.; Anderson, G.M. Physiological Regulation of Leptin as an Integrative Signal of Reproductive Readiness. *Curr. Opin. Pharmacol.* **2022**, *67*, 102321. [CrossRef]
10. Pereira, S.; Cline, D.L.; Glavas, M.M.; Covey, S.D.; Kieffer, T.J. Tissue-Specific Effects of Leptin on Glucose and Lipid Metabolism. *Endocr. Rev.* **2021**, *42*, 1–28. [CrossRef]
11. Li, W.; Liu, Q.; Deng, X.; Chen, Y.; Liu, S.; Story, M. Association between Obesity and Puberty Timing: A Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* **2017**, *14*, 1266. [CrossRef]
12. Vilmann, L.S.; Thisted, E.; Baker, J.L.; Holm, J.-C. Development of Obesity and Polycystic Ovary Syndrome in Adolescents. *Horm. Res. Paediatr.* **2012**, *78*, 269–278. [CrossRef]
13. Rivera, H.M.; Stincic, T.L. Estradiol and the Control of Feeding Behavior. *Steroids* **2018**, *133*, 44–52. [CrossRef]
14. Allan, C.A.; McLachlan, R.I. Androgens and Obesity. *Curr. Opin. Endocrinol. Diabetes Obes.* **2010**, *17*, 224–232. [CrossRef]
15. Pinilla, L.; Aguilar, E.; Dieguez, C.; Millar, R.P.; Tena-Sempere, M. Kisspeptins and Reproduction: Physiological Roles and Regulatory Mechanisms. *Physiol. Rev.* **2012**, *92*, 1235–1316. [CrossRef]
16. Dudek, M.; Ziarniak, K.; Sliwowska, J.H. Kisspeptin and Metabolism: The Brain and Beyond. *Front. Endocrinol.* **2018**, *9*, 145. [CrossRef]
17. Navarro, V.M. Metabolic Regulation of Kisspeptin—The Link between Energy Balance and Reproduction. *Nat. Rev. Endocrinol.* **2020**, *16*, 407–420. [CrossRef]
18. Kotani, M.; Detheux, M.; Vandenbogaerde, A.; Communi, D.; Vanderwinden, J.-M.; Le Poul, E.; Brézillon, S.; Tyldesley, R.; Suarez-Huerta, N.; Vandeput, F.; et al. The Metastasis Suppressor Gene KiSS-1 Encodes Kisspeptins, the Natural Ligands of the Orphan G Protein-Coupled Receptor GPR54. *J. Biol. Chem.* **2001**, *276*, 34631–34636. [CrossRef]
19. Seminara, S.B.; Messager, S.; Chatzidaki, E.E.; Thresher, R.R.; Acierno, J.S.; Shagoury, J.K.; Bo-Abbas, Y.; Kuohung, W.; Schwinof, K.M.; Hendrick, A.G.; et al. The GPR54 Gene as a Regulator of Puberty. *N. Engl. J. Med.* **2003**, *349*, 1614–1627. [CrossRef]
20. de Roux, N.; Genin, E.; Carel, J.-C.; Matsuda, F.; Chaussain, J.-L.; Milgrom, E. Hypogonadotropic Hypogonadism Due to Loss of Function of the KiSS1-Derived Peptide Receptor GPR54. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 10972–10976. [CrossRef] [PubMed]
21. Silveira, L.G.; Noel, S.D.; Silveira-Neto, A.P.; Abreu, A.P.; Brito, V.N.; Santos, M.G.; Bianco, S.D.C.; Kuohung, W.; Xu, S.; Gryngarten, M.; et al. Mutations of the KISS1 Gene in Disorders of Puberty. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 2276–2280. [CrossRef] [PubMed]
22. Topaloglu, A.K.; Tello, J.A.; Kotan, L.D.; Ozbek, M.N.; Yilmaz, M.B.; Erdogan, S.; Gurbuz, F.; Temiz, F.; Millar, R.P.; Yuksel, B. Inactivating KISS1 Mutation and Hypogonadotropic Hypogonadism. *N. Engl. J. Med.* **2012**, *366*, 629–635. [CrossRef] [PubMed]
23. Teles, M.G.; Bianco, S.D.C.; Brito, V.N.; Trarbach, E.B.; Kuohung, W.; Xu, S.; Seminara, S.B.; Mendonca, B.B.; Kaiser, U.B.; Latronico, A.C. A GPR54-Activating Mutation in a Patient with Central Precocious Puberty. *N. Engl. J. Med.* **2008**, *358*, 709–715. [CrossRef]
24. Wakabayashi, Y.; Nakada, T.; Murata, K.; Ohkura, S.; Mogi, K.; Navarro, V.M.; Clifton, D.K.; Mori, Y.; Tsukamura, H.; Maeda, K.-I.; et al. Neurokinin B and Dynorphin A in Kisspeptin Neurons of the Arcuate Nucleus Participate in Generation of Periodic Oscillation of Neural Activity Driving Pulsatile Gonadotropin-Releasing Hormone Secretion in the Goat. *J. Neurosci.* **2010**, *30*, 3124–3132. [CrossRef] [PubMed]
25. Navarro, V.M.; Gottsch, M.L.; Chavkin, C.; Okamura, H.; Clifton, D.K.; Steiner, R.A. Regulation of Gonadotropin-Releasing Hormone Secretion by Kisspeptin/Dynorphin/Neurokinin B Neurons in the Arcuate Nucleus of the Mouse. *J. Neurosci.* **2009**, *29*, 11859–11866. [CrossRef]
26. Quennell, J.H.; Howell, C.S.; Roa, J.; Augustine, R.A.; Grattan, D.R.; Anderson, G.M. Leptin Deficiency and Diet-Induced Obesity Reduce Hypothalamic Kisspeptin Expression in Mice. *Endocrinology* **2011**, *152*, 1541–1550. [CrossRef] [PubMed]
27. Luque, R.M.; Kineman, R.D.; Tena-Sempere, M. Regulation of Hypothalamic Expression of KiSS-1 and GPR54 Genes by Metabolic Factors: Analyses Using Mouse Models and a Cell Line. *Endocrinology* **2007**, *148*, 4601–4611. [CrossRef] [PubMed]
28. Castellano, J.M.; Navarro, V.M.; Fernández-Fernández, R.; Nogueiras, R.; Tovar, S.; Roa, J.; Vazquez, M.J.; Vigo, E.; Casanueva, F.F.; Aguilar, E.; et al. Changes in Hypothalamic KiSS-1 System and Restoration of Pubertal Activation of the Reproductive Axis by Kisspeptin in Undernutrition. *Endocrinology* **2005**, *146*, 3917–3925. [CrossRef]
29. Castellano, J.M.; Navarro, V.M.; Fernández-Fernández, R.; Roa, J.; Vigo, E.; Pineda, R.; Dieguez, C.; Aguilar, E.; Pinilla, L.; Tena-Sempere, M. Expression of Hypothalamic KiSS-1 System and Rescue of Defective Gonadotropic Responses by Kisspeptin in Streptozotocin-Induced Diabetic Male Rats. *Diabetes* **2006**, *55*, 2602–2610. [CrossRef]

30. Fu, L.-Y.; van den Pol, A.N. Kisspeptin Directly Excites Anorexigenic Proopiomelanocortin Neurons but Inhibits Orexigenic Neuropeptide Y Cells by an Indirect Synaptic Mechanism. *J. Neurosci.* **2010**, *30*, 10205–10219. [CrossRef]
31. Villa, P.A.; Ruggiero-Ruff, R.E.; Jamieson, B.B.; Campbell, R.E.; Coss, D. Obesity Alters POMC and Kisspeptin Neuron Cross Talk Leading to Reduced Luteinizing Hormone in Male Mice. *J. Neurosci.* **2024**, *44*, e0222242024. [CrossRef]
32. Backholer, K.; Smith, J.T.; Rao, A.; Pereira, A.; Iqbal, J.; Ogawa, S.; Li, Q.; Clarke, I.J. Kisspeptin Cells in the Ewe Brain Respond to Leptin and Communicate with Neuropeptide Y and Proopiomelanocortin Cells. *Endocrinology* **2010**, *151*, 2233–2243. [CrossRef]
33. Cravo, R.M.; Frazao, R.; Perello, M.; Osborne-Lawrence, S.; Williams, K.W.; Zigman, J.M.; Vianna, C.; Elias, C.F. Leptin Signaling in Kiss1 Neurons Arises after Pubertal Development. *PLoS ONE* **2013**, *8*, e58698. [CrossRef]
34. Egan, O.K.; Inglis, M.A.; Anderson, G.M. Leptin Signaling in AgRP Neurons Modulates Puberty Onset and Adult Fertility in Mice. *J. Neurosci.* **2017**, *37*, 3875–3886. [CrossRef]
35. Smith, J.T.; Acohido, B.V.; Clifton, D.K.; Steiner, R.A. KiSS-1 Neurones Are Direct Targets for Leptin in the Ob/Ob Mouse. *J. Neuroendocr.* **2006**, *18*, 298–303. [CrossRef]
36. True, C.; Kirigiti, M.A.; Kievit, P.; Grove, K.L.; Smith, M.S. Leptin Is Not the Critical Signal for Kisspeptin or Luteinising Hormone Restoration during Exit from Negative Energy Balance. *J. Neuroendocrinol.* **2011**, *23*, 1099–1112. [CrossRef] [PubMed]
37. Patel, R.; Smith, J.T. Novel Actions of Kisspeptin Signaling Outside of GnRH-Mediated Fertility: A Potential Role in Energy Balance. *Domest. Anim. Endocrinol.* **2020**, *73*, 106467. [CrossRef] [PubMed]
38. Stengel, A.; Wang, L.; Goebel-Stengel, M.; Taché, Y. Centrally Injected Kisspeptin Reduces Food Intake by Increasing Meal Intervals in Mice. *Neuroreport* **2011**, *22*, 253–257. [CrossRef] [PubMed]
39. Saito, R.; Tanaka, K.; Nishimura, H.; Nishimura, K.; Sonoda, S.; Ueno, H.; Motojima, Y.; Yoshimura, M.; Maruyama, T.; Yamamoto, Y.; et al. Centrally Administered Kisspeptin Suppresses Feeding via Nesfatin-1 and Oxytocin in Male Rats. *Peptides* **2019**, *112*, 114–124. [CrossRef]
40. Talbi, R.; Laran-Chich, M.-P.; Magoul, R.; El Ouezzani, S.; Simonneaux, V. Kisspeptin and RFRP-3 Differentially Regulate Food Intake and Metabolic Neuropeptides in the Female Desert Jerboa. *Sci. Rep.* **2016**, *6*, 36057. [CrossRef]
41. Tolson, K.P.; Garcia, C.; Yen, S.; Simonds, S.; Stefanidis, A.; Lawrence, A.; Smith, J.T.; Kauffman, A.S. Impaired Kisspeptin Signaling Decreases Metabolism and Promotes Glucose Intolerance and Obesity. *J. Clin. Investig.* **2014**, *124*, 3075–3079. [CrossRef]
42. Padilla, S.L.; Perez, J.G.; Ben-Hamo, M.; Johnson, C.W.; Sanchez, R.E.A.; Bussi, I.L.; Palmiter, R.D.; de la Iglesia, H.O. Kisspeptin Neurons in the Arcuate Nucleus of the Hypothalamus Orchestrate Circadian Rhythms and Metabolism. *Curr. Biol.* **2019**, *29*, 592–604.e4. [CrossRef]
43. Velasco, I.; León, S.; Barroso, A.; Ruiz-Pino, F.; Heras, V.; Torres, E.; León, M.; Ruohonen, S.T.; García-Galiano, D.; Romero-Ruiz, A.; et al. Gonadal Hormone-Dependent vs. -Independent Effects of Kisspeptin Signaling in the Control of Body Weight and Metabolic Homeostasis. *Metabolism* **2019**, *98*, 84–94. [CrossRef] [PubMed]
44. Nestor, C.C.; Bedenbaugh, M.N.; Hileman, S.M.; Coolen, L.M.; Lehman, M.N.; Goodman, R.L. Regulation of GnRH Pulsatility in Ewes. *Reproduction* **2018**, *156*, R83–R99. [CrossRef] [PubMed]
45. Chen, Z.; Si, L.; Shu, W.; Zhang, X.; Wei, C.; Wei, M.; Cheng, L.; Chen, Z.; Qiao, Y.; Yang, S. Exogenous Melatonin Regulates Puberty and the Hypothalamic GnRH-GnIH System in Female Mice. *Brain Sci.* **2022**, *12*, 1550. [CrossRef]
46. Bohlen, T.M.; Silveira, M.A.; Buonfiglio, D.D.C.; Ferreira-Neto, H.C.; Cipolla-Neto, J.; Donato, J.; Frazao, R. A Short-Day Photoperiod Delays the Timing of Puberty in Female Mice via Changes in the Kisspeptin System. *Front. Endocrinol.* **2018**, *9*, 44. [CrossRef] [PubMed]
47. Chen, Z.; Si, L.; Zhang, X.; Wei, C.; Shu, W.; Wei, M.; Cheng, L.; Chen, Z.; Qiao, Y.; Yang, S. Therapeutic Effects of Melatonin in Female Mice with Central Precocious Puberty by Regulating the Hypothalamic Kiss-1/Kiss1R System. *Behav. Brain Res.* **2024**, *461*, 114783. [CrossRef]
48. Avendaño, M.S.; Vazquez, M.J.; Tena-Sempere, M. Disentangling puberty: Novel neuroendocrine pathways and mechanisms for the control of mammalian puberty. *Hum. Reprod. Updat.* **2017**, *23*, 737–763. [CrossRef] [PubMed]
49. Vazquez, M.J.; Toro, C.A.; Castellano, J.M.; Ruiz-Pino, F.; Roa, J.; Beiroa, D.; Heras, V.; Velasco, I.; Dieguez, C.; Pinilla, L.; et al. SIRT1 Mediates Obesity- and Nutrient-Dependent Perturbation of Pubertal Timing by Epigenetically Controlling Kiss1 Expression. *Nat. Commun.* **2018**, *9*, 4194. [CrossRef]
50. Frisch, R.E.; Revelle, R. Height and Weight at Menarche and a Hypothesis of Menarche. *Arch. Dis. Child.* **1971**, *46*, 695–701. [CrossRef]
51. Marino, M.; Di Pietro, P.; D'Auria, R.; Lombardi, M.; Pastorino, G.M.G.; Troisi, J.; Operto, F.F.; Carrizzo, A.; Vecchione, C.; Viggiano, A.; et al. Adult Neurogenesis Is Regulated by the Endocannabinoid and Kisspeptin Systems. *Int. J. Mol. Sci.* **2025**, *26*, 3977. [CrossRef]
52. Majarune, S.; Nima, P.; Sugimoto, A.; Nagae, M.; Inoue, N.; Tsukamura, H.; Uenoyama, Y. Ad Libitum Feeding Triggers Puberty Onset Associated with Increases in Arcuate Kiss1 and Pdyn Expression in Growth-Retarded Rats. *J. Reprod. Dev.* **2019**, *65*, 397–406. [CrossRef]

53. D'Angelo, S.; Mele, E.; Di Filippo, F.; Viggiano, A.; Meccariello, R. Sirt1 Activity in the Brain: Simultaneous Effects on Energy Homeostasis and Reproduction. *Int. J. Environ. Res. Public Health* **2021**, *18*, 1243. [CrossRef]
54. Ruggiero, M.; Motti, M.L.; Meccariello, R.; Mazzeo, F. Resveratrol and Physical Activity: A Successful Combination for the Maintenance of Health and Wellbeing? *Nutrients* **2025**, *17*, 837. [CrossRef] [PubMed]
55. Leon, S.; Talbi, R.; McCarthy, E.A.; Ferrari, K.; Fergani, C.; Naule, L.; Choi, J.H.; Carroll, R.S.; Kaiser, U.B.; Aylwin, C.F.; et al. Sex-Specific Pubertal and Metabolic Regulation of Kiss1 Neurons via Nhlh2. *eLife* **2021**, *10*, e69765. [CrossRef] [PubMed]
56. Hudson, A.D.; Kauffman, A.S. Metabolic Actions of Kisspeptin Signaling: Effects on Body Weight, Energy Expenditure, and Feeding. *Pharmacol. Ther.* **2022**, *231*, 107974. [CrossRef]
57. Meccariello, R.; Fasano, S.; Pierantoni, R. Kisspeptins, New Local Modulators of Male Reproduction: A Comparative Overview. *Gen. Comp. Endocrinol.* **2020**, *299*, 113618. [CrossRef]
58. Meccariello, R. The Kisspeptin System in Male Reproduction. *Endocrines* **2022**, *3*, 168–174. [CrossRef]
59. Sharma, A.; Thaventhiran, T.; Minhas, S.; Dhillo, W.S.; Jayasena, C.N. Kisspeptin and Testicular Function—Is it Necessary? *Int. J. Mol. Sci.* **2020**, *21*, 2958. [CrossRef]
60. Ricci, G.; Guillou, F.; Catizone, A.; Mele, V.G.; Moggio, M.; Chioccarelli, T.; Diano, N.; Meccariello, R.; Pierantoni, R.; Fasano, S.; et al. KISS1R and ANKRD31 Cooperate to Enhance Leydig Cell Gene Expression via the Cytoskeletal-Nucleoskeletal Pathway. *Front. Cell Dev. Biol.* **2022**, *10*, 877270. [CrossRef]
61. Ramzan, F.; Qureshi, I.Z.; Ramzan, M.H. Dose-Dependent Degeneration of Leydig Cells Following Kisspeptin-10 Administration: An Ultrastructural Study. *Protein Pept. Lett.* **2022**, *29*, 64–70. [CrossRef]
62. Petrucci, L.; Maranesi, M.; Verini Supplizi, A.; Dall'Aglio, C.; Mandara, M.T.; Quassinti, L.; Bramucci, M.; Miano, A.; Gobbetti, A.; Catone, G.; et al. Kisspeptin/GnRH1 system in Leydig cells of horse (*Equus caballus*): Presence and function. *Theriogenology* **2020**, *152*, 1–7. [CrossRef]
63. Marino, M.; D'Auria, R.; Mele, E.; Pastorino, G.M.G.; Di Pietro, P.; D'Angelo, S.; Della Rocca, N.; Operto, F.F.; Vecchione, C.; Fasano, S.; et al. The Interplay between Kisspeptin and Endocannabinoid Systems Modulates Male Hypothalamic and Gonadic Control of Reproduction in Vivo. *Front. Endocrinol.* **2023**, *14*, 1269334. [CrossRef]
64. Ciaramella, V.; Meccariello, R.; Chioccarelli, T.; Sirleto, M.; Fasano, S.; Pierantoni, R.; Chianese, R. Anandamide Acts via Kisspeptin in the Regulation of Testicular Activity of the Frog, Pelophylax Esculentus. *Mol. Cell. Endocrinol.* **2016**, *420*, 75–84. [CrossRef] [PubMed]
65. Chianese, R.; Ciaramella, V.; Fasano, S.; Pierantoni, R.; Meccariello, R. Kisspeptin Drives Germ Cell Progression in the Anuran Amphibian Pelophylax Esculentus: A Study Carried out in Ex Vivo Testes. *Gen. Comp. Endocrinol.* **2015**, *211*, 81–91. [CrossRef]
66. Chianese, R.; Ciaramella, V.; Fasano, S.; Pierantoni, R.; Meccariello, R. Kisspeptin Regulates Steroidogenesis and Spermiation in Anuran Amphibian. *Reproduction* **2017**, *154*, 403–414. [CrossRef]
67. Santoro, A.; Mele, E.; Marino, M.; Viggiano, A.; Nori, S.L.; Meccariello, R. The Complex Interplay between Endocannabinoid System and the Estrogen System in Central Nervous System and Periphery. *Int. J. Mol. Sci.* **2021**, *22*, 972. [CrossRef] [PubMed]
68. Barchi, M.; Innocenzi, E.; Giannattasio, T.; Dolci, S.; Rossi, P.; Grimaldi, P. Cannabinoid Receptors Signaling in the Development, Epigenetics, and Tumours of Male Germ Cells. *Int. J. Mol. Sci.* **2019**, *21*, 25. [CrossRef]
69. Leeners, B.; Geary, N.; Tobler, P.N.; Asarian, L. Ovarian Hormones and Obesity. *Hum. Reprod. Update* **2017**, *23*, 300–321. [CrossRef]
70. Mahboobifard, F.; Pourgholami, M.H.; Jorjani, M.; Dargahi, L.; Amiri, M.; Sadeghi, S.; Tehrani, F.R. Estrogen as a Key Regulator of Energy Homeostasis and Metabolic Health. *Biomed. Pharmacother.* **2022**, *156*, 113808. [CrossRef]
71. Mazzeo, F.; Meccariello, R. Cannabis and Paternal Epigenetic Inheritance. *Int. J. Environ. Res. Public Health* **2023**, *20*, 5663. [CrossRef] [PubMed]
72. Leisegang, K.; Sengupta, P.; Agarwal, A.; Henkel, R. Obesity and Male Infertility: Mechanisms and Management. *Andrologia* **2021**, *53*, e13617. [CrossRef] [PubMed]
73. Tajar, A.; Forti, G.; O'Neill, T.W.; Lee, D.M.; Silman, A.J.; Finn, J.D.; Bartfai, G.; Boonen, S.; Casanueva, F.F.; Giwercman, A.; et al. Characteristics of Secondary, Primary, and Compensated Hypogonadism in Aging Men: Evidence from the European Male Ageing Study. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 1810–1818. [CrossRef]
74. Andreozzi, F.; Mannino, G.C.; Mancuso, E.; Spiga, R.; Perticone, F.; Sesti, G. Plasma Kisspeptin Levels Are Associated with Insulin Secretion in Nondiabetic Individuals. *PLoS ONE* **2017**, *12*, e0179834. [CrossRef]
75. Asare-Anane, H.; Ofori, E.K.; Kwao-Zigah, G.; Ateko, R.O.; Annan, B.D.R.T.; Adjei, A.B.; Quansah, M. Lower Circulating Kisspeptin and Primary Hypogonadism in Men with Type 2 Diabetes. *Endocrinol. Diabetes Metab.* **2019**, *2*, e00070. [CrossRef]
76. Izzi-Engbeaya, C.; Comninos, A.N.; Clarke, S.A.; Jomard, A.; Yang, L.; Jones, S.; Abbara, A.; Narayanaswamy, S.; Eng, P.C.; Papadopoulou, D.; et al. The Effects of Kisspeptin on β-Cell Function, Serum Metabolites and Appetite in Humans. *Diabetes Obes. Metab.* **2018**, *20*, 2800–2810. [CrossRef]
77. Celik, O.; Yildiz, B.O. Obesity and Physical Exercise. *Minerva Endocrinol.* **2021**, *46*, 131–144. [CrossRef] [PubMed]

78. Gonzalez-Gil, A.M.; Elizondo-Montemayor, L. The Role of Exercise in the Interplay between Myokines, Hepatokines, Osteokines, Adipokines, and Modulation of Inflammation for Energy Substrate Redistribution and Fat Mass Loss: A Review. *Nutrients* **2020**, *12*, 1899. [CrossRef]
79. Rocliffe, P.; Adamakis, M.; O'Keeffe, B.T.; Walsh, L.; Bannon, A.; Garcia-Gonzalez, L.; Chambers, F.; Stylianou, M.; Sherwin, I.; Mannix-McNamara, P.; et al. The Impact of Typical School Provision of Physical Education, Physical Activity and Sports on Adolescent Mental Health and Wellbeing: A Systematic Literature Review. *Adolesc. Res. Rev.* **2024**, *9*, 339–364. [CrossRef]
80. Guthold, R.; Stevens, G.A.; Riley, L.M.; Bull, F.C. Global Trends in Insufficient Physical Activity among Adolescents: A Pooled Analysis of 298 Population-Based Surveys with 1·6 Million Participants. *Lancet Child Adolesc. Health* **2020**, *4*, 23–35. [CrossRef] [PubMed]
81. Northey, J.M.; Cherbuin, N.; Pumpa, K.L.; Smee, D.J.; Rattray, B. Exercise Interventions for Cognitive Function in Adults Older than 50: A Systematic Review with Meta-Analysis. *Br. J. Sports Med.* **2018**, *52*, 154–160. [CrossRef] [PubMed]
82. Andreato, L.V.; Esteves, J.V.; Coimbra, D.R.; Moraes, A.J.P.; de Carvalho, T. The Influence of High-Intensity Interval Training on Anthropometric Variables of Adults with Overweight or Obesity: A Systematic Review and Network Meta-Analysis. *Obes. Rev.* **2019**, *20*, 142–155. [CrossRef]
83. Baptista, F.M.; Andias, R.; Rocha, N.P.; Silva, A.G. A Practice Guide for Physical Therapists Prescribing Physical Exercise for Older Adults. *J. Aging Phys. Act.* **2024**, *32*, 771–783. [CrossRef] [PubMed]
84. Shen, Y.; Shi, Q.; Nong, K.; Li, S.; Yue, J.; Huang, J.; Dong, B.; Beauchamp, M.; Hao, Q. Exercise for Sarcopenia in Older People: A Systematic Review and Network Meta-Analysis. *J. Cachexia Sarcopenia Muscle* **2023**, *14*, 1199–1211. [CrossRef]
85. Davenport, M.H.; Meah, V.L.; Ruchat, S.-M.; Davies, G.A.; Skow, R.J.; Barrowman, N.; Adamo, K.B.; Poitras, V.J.; Gray, C.E.; Jaramillo Garcia, A.; et al. Impact of Prenatal Exercise on Neonatal and Childhood Outcomes: A Systematic Review and Meta-Analysis. *Br. J. Sports Med.* **2018**, *52*, 1386–1396. [CrossRef]
86. Mottola, M.F.; Davenport, M.H.; Ruchat, S.-M.; Davies, G.A.; Poitras, V.J.; Gray, C.E.; Garcia, A.J.; Barrowman, N.; Adamo, K.B.; Duggan, M.; et al. 2019 Canadian Guideline for Physical Activity throughout Pregnancy. *Br. J. Sports Med.* **2018**, *52*, 1339–1346. [CrossRef]
87. Ribeiro, M.M.; Andrade, A.; Nunes, I. Physical Exercise in Pregnancy: Benefits, Risks and Prescription. *J. Perinat. Med.* **2022**, *50*, 4–17. [CrossRef]
88. Gallotta, M.C.; Franciosi, E.; Giorgi, M.; Guidetti, L.; Cerbara, E.; Pes, G.; Silvestri, F.; Curzi, D. Benefits of Inclusive Sport Training on Fitness and Health of Athletes with and without Intellectual Disability. *Sci. Rep.* **2024**, *14*, 21203. [CrossRef]
89. Diz, S.; Jacinto, M.; Costa, A.M.; Monteiro, D.; Matos, R.; Antunes, R. Physical Activity, Quality of Live and Well-Being in Individuals with Intellectual and Developmental Disability. *Healthcare* **2024**, *12*, 654. [CrossRef]
90. Collado-Mateo, D.; Lavín-Pérez, A.M.; Peñacoba, C.; Del Coso, J.; Leyton-Román, M.; Luque-Casado, A.; Gasque, P.; Fernández-Del-Olmo, M.Á.; Amado-Alonso, D. Key Factors Associated with Adherence to Physical Exercise in Patients with Chronic Diseases and Older Adults: An Umbrella Review. *Int. J. Environ. Res. Public. Health.* **2021**, *18*, 2023. [CrossRef] [PubMed]
91. Araujo, D.N.; Ribeiro, C.T.; Maciel, A.C.; Bruno, S.S.; Fregonezi, G.A.; Dias, F.A. Physical Exercise for the Treatment of Non-Ulcerated Chronic Venous Insufficiency. *Cochrane Database Syst. Rev.* **2023**, *6*, CD010637. [CrossRef] [PubMed]
92. Tucker, W.J.; Fegers-Wustrow, I.; Halle, M.; Haykowsky, M.J.; Chung, E.H.; Kovacic, J.C. Exercise for Primary and Secondary Prevention of Cardiovascular Disease: JACC Focus Seminar 1/4. *J. Am. Coll. Cardiol.* **2022**, *80*, 1091–1106. [CrossRef] [PubMed]
93. WHO. Guidelines on Physical Activity and Sedentary Behaviour. 2020. Available online: https://www.who.int/publications/i/item/9789240015128 (accessed on 15 July 2025).
94. Kadowaki, T.; Yamauchi, T.; Kubota, N.; Hara, K.; Ueki, K.; Tobe, K. Adiponectin and Adiponectin Receptors in Insulin Resistance, Diabetes, and the Metabolic Syndrome. *J. Clin. Investig.* **2006**, *116*, 1784–1792. [CrossRef]
95. Bouassida, A.; Chamari, K.; Zaouali, M.; Feki, Y.; Zbidi, A.; Tabka, Z. Review on Leptin and Adiponectin Responses and Adaptations to Acute and Chronic Exercise. *Br. J. Sports Med.* **2010**, *44*, 620–630. [CrossRef]
96. Martinez-Huenchullan, S.F.; Tam, C.S.; Ban, L.A.; Ehrenfeld-Slater, P.; Mclennan, S.V.; Twigg, S.M. Skeletal Muscle Adiponectin Induction in Obesity and Exercise. *Metabolism* **2020**, *102*, 154008. [CrossRef]
97. Sagheb, M.M.; Azarpira, N.; Yaghobi, R. The Effect of Leptin and Adiponectin on KiSS-1 and KissR mRNA Expression in Rat Islets of Langerhans and CRI-D2 Cell Line. *Int. J. Endocrinol. Metab.* **2014**, *12*, e15297. [CrossRef]
98. Wen, J.-P.; Liu, C.; Bi, W.-K.; Hu, Y.-T.; Chen, Q.; Huang, H.; Liang, J.-X.; Li, L.-T.; Lin, L.-X.; Chen, G. Adiponectin Inhibits KISS1 Gene Transcription through AMPK and Specificity Protein-1 in the Hypothalamic GT1-7 Neurons. *J. Endocrinol.* **2012**, *214*, 177–189. [CrossRef]
99. Mlyczyńska, E.; Kieżun, M.; Kurowska, P.; Dawid, M.; Pich, K.; Respekta, N.; Daudon, M.; Rytelewska, E.; Dobrzyń, K.; Kamińska, B.; et al. New Aspects of Corpus Luteum Regulation in Physiological and Pathological Conditions: Involvement of Adipokines and Neuropeptides. *Cells* **2022**, *11*, 957. [CrossRef] [PubMed]
100. Liang, C.; Li, X.; Song, G.; Schmidt, S.F.; Sun, L.; Chen, J.; Pan, X.; Zhao, H.; Yan, Y. Adipose Kiss1 Controls Aerobic Exercise-Related Adaptive Responses in Adipose Tissue Energy Homeostasis. *FASEB J.* **2024**, *38*, e23743. [CrossRef]

101. Arisha, A.H.; Moustafa, A. Potential Inhibitory Effect of Swimming Exercise on the Kisspeptin-GnRH Signaling Pathway in Male Rats. *Theriogenology* **2019**, *133*, 87–96. [CrossRef]
102. Xu, R.; Feng, J.; Liang, C.; Song, G.; Yan, Y. Effects of High-Fat Diet and Treadmill Running on the Hypothalamic Kiss-1-GPR54 Signaling Pathway in Male Growing Rats. *Hormones* **2022**, *21*, 641–652. [CrossRef]
103. Kacar, E.; Bulmus, O.; Ercan, Z.; Kavuran, I.B.; Zorlu, G.; Tan, F.; Serhatlioglu, I.; Kelestimur, H. Treadmill Exercise Has Healing Effects on Obesity-Induced Sexual Behavior Disorder through Kisspeptin and kiss1R Expression in Male Rats. *Cell. Mol. Biol.* **2023**, *69*, 8–12. [CrossRef] [PubMed]
104. Chang, B.; Song, C.; Gao, H.; Ma, T.; Li, T.; Ma, Q.; Yao, T.; Wang, M.; Li, J.; Yi, X.; et al. Leptin and Inflammatory Factors Play a Synergistic Role in the Regulation of Reproduction in Male Mice through Hypothalamic Kisspeptin-Mediated Energy Balance. *Reprod. Biol. Endocrinol.* **2021**, *19*, 12. [CrossRef] [PubMed]
105. Obradovic, M.; Sudar-Milovanovic, E.; Soskic, S.; Essack, M.; Arya, S.; Stewart, A.J.; Gojobori, T.; Isenovic, E.R. Leptin and Obesity: Role and Clinical Implication. *Front. Endocrinol.* **2021**, *12*, 585887. [CrossRef]
106. Pereira, B.C.; da Rocha, A.L.; Pauli, J.R.; Ropelle, E.R.; de Souza, C.T.; Cintra, D.E.; Sant'Ana, M.R.; da Silva, A.S.R. Excessive Eccentric Exercise Leads to Transitory Hypothalamic Inflammation, Which May Contribute to the Low Body Weight Gain and Food Intake in Overtrained Mice. *Neuroscience* **2015**, *311*, 231–242. [CrossRef]
107. Khajehnasiri, N.; Khazali, H.; Sheikhzadeh, F. Various Responses of Male Pituitary-Gonadal Axis to Different Intensities of Long-Term Exercise: Role of Expression of KNDY-related Genes. *J. Biosci.* **2018**, *43*, 569–574. [CrossRef]
108. Yi, X.; Gao, H.; Chen, D.; Tang, D.; Huang, W.; Li, T.; Ma, T.; Chang, B. Effects of Obesity and Exercise on Testicular Leptin Signal Transduction and Testosterone Biosynthesis in Male Mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2017**, *312*, R501–R510. [CrossRef] [PubMed]
109. Rosety, M.Á.; Díaz, A.J.; Rosety, J.M.; Pery, M.T.; Brenes-Martín, F.; Bernardi, M.; García, N.; Rosety-Rodríguez, M.; Ordoñez, F.J.; Rosety, I. Exercise Improved Semen Quality and Reproductive Hormone Levels in Sedentary Obese Adults. *Nutr. Hosp.* **2017**, *34*, 603–607. [CrossRef]
110. Eisenberg, M.L.; Sapra, K.J.; Kim, S.D.; Chen, Z.; Louis, G.M.B. Semen Quality and Pregnancy Loss in a Contemporary Cohort of Couples Recruited before Conception: Data from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study. *Fertil. Steril.* **2017**, *108*, 613–619. [CrossRef]
111. Rafiee, B.; Morowvat, M.H.; Rahimi-Ghalati, N. Comparing the Effectiveness of Dietary Vitamin C and Exercise Interventions on Fertility Parameters in Normal Obese Men. *Urol. J.* **2016**, *13*, 2635–2639.
112. Wise, L.A.; Wang, T.R.; Ulrichsen, S.P.; Krivorotko, D.; Mikkelsen, E.M.; Kuriyama, A.S.; Laursen, A.S.D.; Jørgensen, M.D.; Eisenberg, M.L.; Rothman, K.J.; et al. A Prospective Study of Male Physical Activity and Fecundability. *Hum. Reprod.* **2025**, *40*, 360–371. [CrossRef]
113. Bird, S.R.; Goebel, C.; Burke, L.M.; Greaves, R.F. Doping in Sport and Exercise: Anabolic, Ergogenic, Health and Clinical Issues. *Ann. Clin. Biochem.* **2016**, *53*, 196–221. [CrossRef] [PubMed]
114. Mazzeo, F.; Raiola, G. An Investigation of Drugs Abuse in Sport Performance. *J. Hum. Sport Exerc.* **2018**, *13*, S309–S319. [CrossRef]
115. Ihalainen, J.K.; Mikkonen, R.S.; Ackerman, K.E.; Heikura, I.A.; Mjøsund, K.; Valtonen, M.; Hackney, A.C. Beyond Menstrual Dysfunction: Does Altered Endocrine Function Caused by Problematic Low Energy Availability Impair Health and Sports Performance in Female Athletes? *Sports Med.* **2024**, *54*, 2267–2289. [CrossRef]
116. McQuilliam, S.J.; Clark, D.R.; Erskine, R.M.; Brownlee, T.E. Free-Weight Resistance Training in Youth Athletes: A Narrative Review. *Sports Med.* **2020**, *50*, 1567–1580. [CrossRef]
117. Oosthuyse, T.; Strauss, J.A.; Hackney, A.C. Understanding the female athlete: Molecular mechanisms underpinning menstrual phase differences in exercise metabolism. *Eur. J. Appl. Physiol.* **2023**, *123*, 423–450. [CrossRef]
118. Mazzeo, F.; Volpe, A.R. From Gene Doping to Athlete Biological Passport. *Sport. Sci.* **2016**, *9*, 97–103.
119. Kim, G.L.; Dhillon, S.S.; Belsham, D.D. Kisspeptin Directly Regulates Neuropeptide Y Synthesis and Secretion via the ERK1/2 and P38 Mitogen-Activated Protein Kinase Signaling Pathways in NPY-Secreting Hypothalamic Neurons. *Endocrinology* **2010**, *151*, 5038–5047. [CrossRef] [PubMed]
120. Yeager, K.K.; Agostini, R.; Nattiv, A.; Drinkwater, B. The Female Athlete Triad: Disordered Eating, Amenorrhea, Osteoporosis. *Med. Sci. Sports Exerc.* **1993**, *25*, 775–777. [CrossRef] [PubMed]
121. Murray, S.B.; Rieger, E.; Touyz, S.W.; De la Garza García Lic, Y. Muscle Dysmorphia and the DSM-V Conundrum: Where Does It Belong? A Review Paper. *Int. J. Eat. Disord.* **2010**, *43*, 483–491. [CrossRef] [PubMed]
122. Mountjoy, M.; Sundgot-Borgen, J.; Burke, L.; Carter, S.; Constantini, N.; Lebrun, C.; Meyer, N.; Sherman, R.; Steffen, K.; Budgett, R.; et al. The IOC Consensus Statement: Beyond the Female Athlete Triad--Relative Energy Deficiency in Sport (RED-S). *Br. J. Sports Med.* **2014**, *48*, 491–497. [CrossRef]
123. Montesano, P.; Di Silvestro, M.; Cipriani, G.; Mazzeo, F. Overtraining Syndrome, Stress and Nutrition in Football Amateur Athletes. *J. Hum. Sport Exerc.* **2019**, *14*, S957–S969. [CrossRef]

124. Adelowo, O.E.; Akindele, B.M.; Adegbola, C.A.; Oyedokun, P.A.; Akhigbe, T.M.; Akhigbe, R.E. Unraveling the Complexity of the Impact of Physical Exercise on Male Reproductive Functions: A Review of Both Sides of a Coin. *Front. Physiol.* **2024**, *15*, 1492771. [CrossRef] [PubMed]
125. Mazzeo, F.; Tafuri, D. Hormone and Metabolic Modulators, Combined Pill and Progestogen Only Pill in Sport: Study of Their Use. *Acta Medica Mediterr.* **2020**, *36*, 443–446.
126. Mazzeo, F. Anabolic Steroid Use in Sports and in Physical Activity: Overview and Analysis. *Sport Mont* **2018**, *16*, 113–118. [CrossRef]
127. Bhasin, S.; Storer, T.W.; Berman, N.; Callegari, C.; Clevenger, B.; Phillips, J.; Bunnell, T.J.; Tricker, R.; Shirazi, A.; Casaburi, R. The Effects of Supraphysiologic Doses of Testosterone on Muscle Size and Strength in Normal Men. *N. Engl. J. Med.* **1996**, *335*, 1–7. [CrossRef] [PubMed]
128. Luque, R.M.; Córdoba-Chacón, J.; Gahete, M.D.; Navarro, V.M.; Tena-Sempere, M.; Kineman, R.D.; Castaño, J.P. Kisspeptin Regulates Gonadotroph and Somatotroph Function in Nonhuman Primate Pituitary via Common and Distinct Signaling Mechanisms. *Endocrinology* **2011**, *152*, 957–966. [CrossRef] [PubMed]
129. Jayasena, C.N.; Comninos, A.N.; Narayanaswamy, S.; Bhalla, S.; Abbara, A.; Ganiyu-Dada, Z.; Busbridge, M.; Ghatei, M.A.; Bloom, S.R.; Dhillo, W.S. Acute and Chronic Effects of Kisspeptin-54 Administration on GH, Prolactin and TSH Secretion in Healthy Women. *Clin. Endocrinol.* **2014**, *81*, 891–898. [CrossRef]
130. Foradori, C.D.; Whitlock, B.K.; Daniel, J.A.; Zimmerman, A.D.; Jones, M.A.; Read, C.C.; Steele, B.P.; Smith, J.T.; Clarke, I.J.; Elsasser, T.H.; et al. Kisspeptin Stimulates Growth Hormone Release by Utilizing Neuropeptide Y Pathways and Is Dependent on the Presence of Ghrelin in the Ewe. *Endocrinology* **2017**, *158*, 3526–3539. [CrossRef]
131. WADA Investigations into the Metabolism and Analysis of Kisspeptin and Analogs for Doping Controls by Means of LC-MS. Available online: https://www.wada-ama.org/en/resources/scientific-research/investigations-metabolism-and-analysis-kisspeptin-and-analogs-doping (accessed on 15 July 2025).
132. Mazzeo, F. Current Concept of Obesity. *Sport. Sci.* **2016**, *9*, 42–48.
133. Marques, P.; De Sousa Lages, A.; Skorupskaite, K.; Rozario, K.S.; Anderson, R.A.; George, J.T. Physiology of GnRH and Gonadotrophin Secretion. In *Endotext*; Feingold, K.R., Ahmed, S.F., Anawalt, B., Blackman, M.R., Boyce, A., Chrousos, G., Corpas, E., de Herder, W.W., Dhatariya, K., Dungan, K., et al., Eds.; MDText.com, Inc.: South Dartmouth, MA, USA, 2000.
134. Pinto, F.M.; Cejudo-Román, A.; Ravina, C.G.; Fernández-Sánchez, M.; Martín-Lozano, D.; Illanes, M.; Tena-Sempere, M.; Candenas, M.L. Characterization of the Kisspeptin System in Human Spermatozoa. *Int. J. Androl.* **2012**, *35*, 63–73. [CrossRef] [PubMed]
135. Montesano, P.; Mazzeo, F. Improvement in Soccer Learning and Methodology for Young Athletes. *J. Phys. Educ. Sport* **2019**, *19*, 795–801. [CrossRef]
136. Mazzeo, F.; Altavilla, G.; D'elia, F.; Raiola, G. Development of Doping in Sports: Overview and Analysis. *J. Phys. Educ. Sport* **2018**, *18*, 1669–1677. [CrossRef]
137. Colpaert, T.; Risseeuw, M.; Deventer, K.; Van Eenoo, P. Investigating the detection of the novel doping-relevant peptide kisspeptin-10 in urine using liquid chromatography high-resolution mass spectrometry. *Biomed. Chromatogr.* **2024**, *38*, e5946. [CrossRef] [PubMed]