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MOLECULAR INSIGHTS INTO SERTOLI CELL FUNCTION: THE IMPACT OF METABOLIC DISORDERS IN CHILDREN AND ADOLESCENTS ON SPERMATOGENIC POTENTIAL

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ABSTRACT

Reduced fertility in males is one of the significant and pertinent health issues throughout the world, including several etiologies of which remain elusive in about half of the man. The male human total sperm count has decreased in past forty years, rising incidence of childhood obesity also couldn't be fortuitous. Here, the molecular pathways by which childhood and adolescent obesity could disrupt future testosterone production are explained. Several mechanisms related with obesity which occurs in obesity may against the complicated exquisite metabolic cross talks that take place in testicular level during child and adolescent provide base to extrapolate the childhood obesity with low sperm density in adults. The International WHO studies show that since 1975, the prevalence level of heavy and obesity has soared worldwide, three folds. These issues are particularly alarming in children, with over 340 million young individuals aged 5 to 19 classified as overweight or obese as of 2016. When excess body fat accumulates, fat cells release pro-inflammatory cytokines and free fatty acids, triggering low-level, ongoing inflammation. This inflammation interferes with the body's insulin usage, resulting in insulin resistance. Consequently, being overweight or obese is a key contributor to insulin resistance, prompting pancreatic β-cells to produce more insulin and leading to hyperinsulinemia. The present overview focuses on the influences of obesity in FSH, IGF system, and androgen/estrogen pathways with regard to SC function and the 'extracellular' 'niche'. Here they discuss how the molecular disruptions observed in obese as well as insulin resistant individuals could obstruct the principal signaling pathways which are otherwise necessary for SCs and GCs growth and differentiation and hence in adiposity-linked low sperm density risk during adulthood from childhood. Recent studies suggest that overweight or obesity can impact with negative effects the male reproductive system. Many investigations have described a correlation between increased body mass and reduced sperm quality. Epidemiological data also show that for the past 40 years sperm concentrations have reduced, pediatric obesity has increased indicating that there is a correlation between the two events. However, the relationship between childhood and adolescent obesity and possible adulthood male infertility has not been well understood and explored by linking intermediary steps.

Keywords: *Follicle-stimulating hormone (FSH), IGF system, Sertoli cell, gut hormones, hyperglycemia, hyperinsulinemia.*

INTRODUCTION

FSH-MEDIATED MOLECULAR SIGNALING PATHWAYS:

Follicle-stimulating hormone (FSH) is a glycoprotein dimer composed of two polypeptide chains: an α chain and a β chain. FSHR shows homologous α subunit to other pituitary hormones whilst, β subunit interacts with FSHR. Positionally, FSHR is implicit integrated within the surface membrane of Sertoli cells (SCs); FSH and FSHR are known to be essential in SC proliferation, differentiation and actualization of the process of apoptosis. This regulation is essential for maintaining the spermatogonial pool by supporting SC maintenance, differentiation, and survival, with SCs responding to FSH based on their developmental phase. In fetal and early postnatal stages, FSH drives SC proliferation, determining their total count. However, as puberty nears, SCs lose their capacity to proliferate, and FSH instead aids in their maturation(Cannarella et al., 2024; Tao et al., 2021).

FSH influences Sertoli cell functions, including proliferation, differentiation, and apoptosis, especially by triggering cell proliferation during early postnatal life. This process is regulated through the cAMP/PKA pathway, ERK/MAPK pathway, and PI3K/Akt/mTORC1 pathway, as studies have shown increased [3H]-thymidine incorporation in immature SCs with dibutyryl-cAMP (db-cAMP) treatment. FSH association with its G protein coupled FSHR activates the cAMP/PKA pathways and CREB is phosphorylated at the target gene promoter containing CREs to influence gene expression(Brix et al., 2023; Pereira et al., 2021).

In addition, the FSHR-Gαs coupling promotes the activation of ERK/MAPK signaling cascade in a cAMP/PKA-dependent signaling mechanism or through the FSHR-Gαi subunits signaling in an Src-mediated manner. ERK then phases CREB which binds to CRE enabling gene expression to enhanced (Cannarella et al., 2019) . Hence during SC proliferation, the PI3k/Akt/mTOR signaling promotes structure of the proteins that helps in DNA replication and important enzymes in cell cycle like c-Myc and Cyclin-D1. The differentiation phase, marking puberty, follows SC mitosis(Brix et al., 2023).

At this point, SCs express AR and LH-driven testosterone increases, forming the blood-testis barrier (BTB), segregating SSCs, and promoting cytoplasmic membrane changes. FSHR's coupling to the Gαs subunit activates the cAMP/PKA pathway, while interactions with Gαi and Gβγ subunits trigger the ERK/MAPK and PI3K/AKT/mTOR pathways, respectively(Crépieux et al., 2001). FSH also activates the calcium and PLA2 pathways, and IGF1R signaling, linking with PP1 to affect BTB dynamics(Crespo et al., 2020).

FSH seems to function by upregulating Hypoxia Inducible Factor 2 (HIF2). While the levels of tight junction proteins like ZO-1, ZO-2, Occludin, and Claudin-11 increase in the blood-testis barrier (BTB), the remodeling process involves the activity of Tissue Plasminogen Activator (TPA) (Long et al., 2018). Follicle-stimulating Hormone (FSH) plays a key role in male fertility by increasing calcium influx, which raises intracellular Ca^{2+} levels. This elevation triggers pathways that impact the cytoskeletal structure of Sertoli cells (SCs). FSH also supports spermatogonia by promoting an environment rich in growth factors, nutrients, and essential molecules for spermatogonial stem cells (SSCs) (Zhang et al., 2006).

Research shows that disruptions in FSH signaling can limit SSC proliferation and maturation, while FSH-driven production of factors like GDNF and FGF2 encourages SSC self-renewal. Activation of the PLA2 pathway by FSH boosts the secretion of PGE2, which supports SSC self-renewal and prevents premature differentiation. Additionally, FSH influences the release of SCF, which is crucial for SSC differentiation and maturation(Crespo et al., 2020).

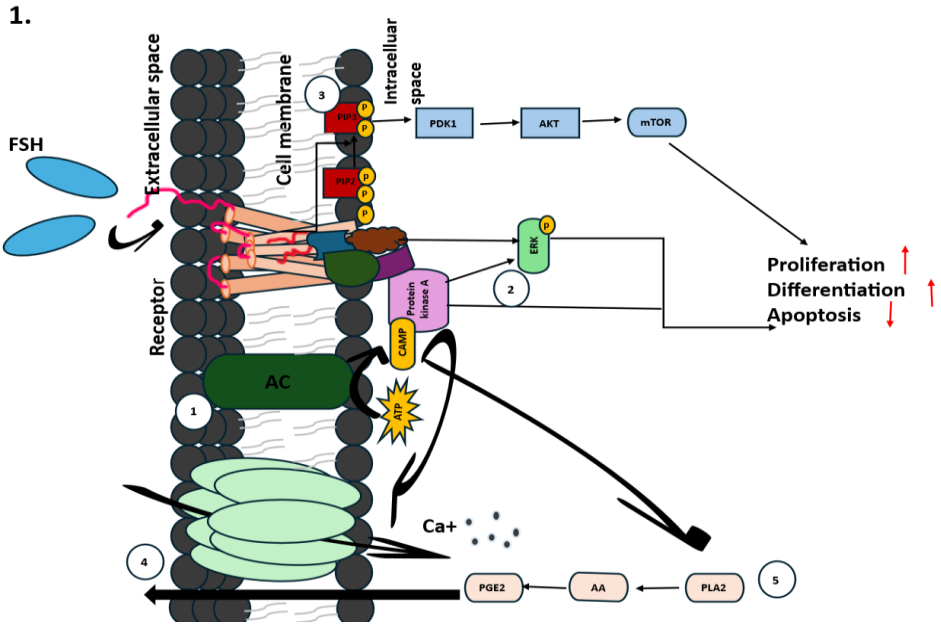

Fig 1. Molecular signaling pathways activated by follicle-stimulating hormone (FSH) in Sertoli cells.

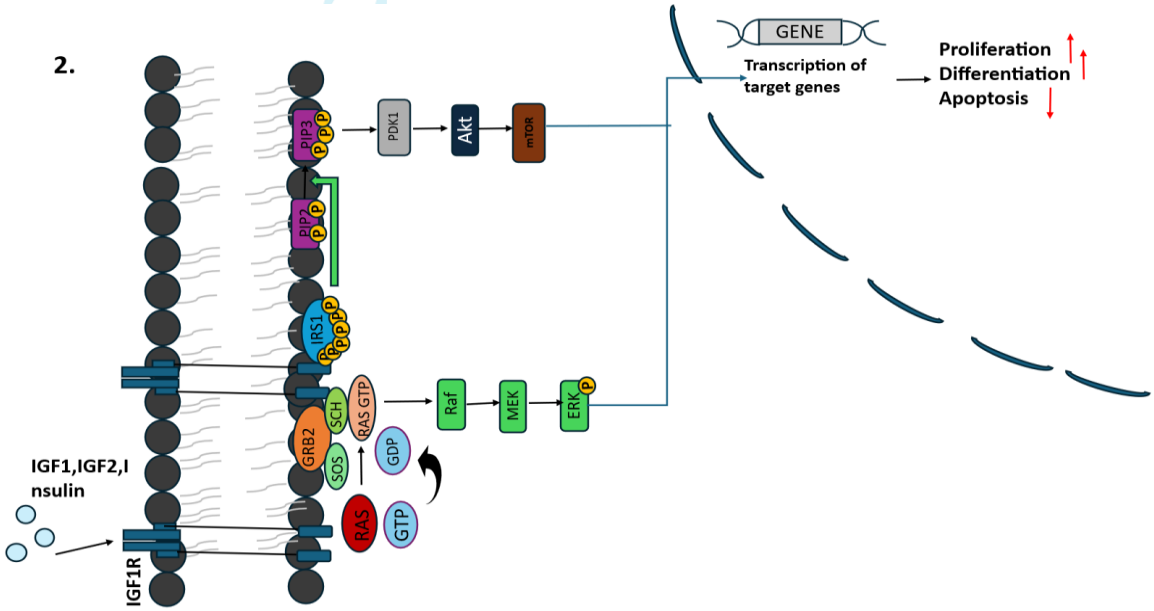

Fig 2. Insulin and insulin-like growth factor (IGF) signaling pathways in Sertoli cells.

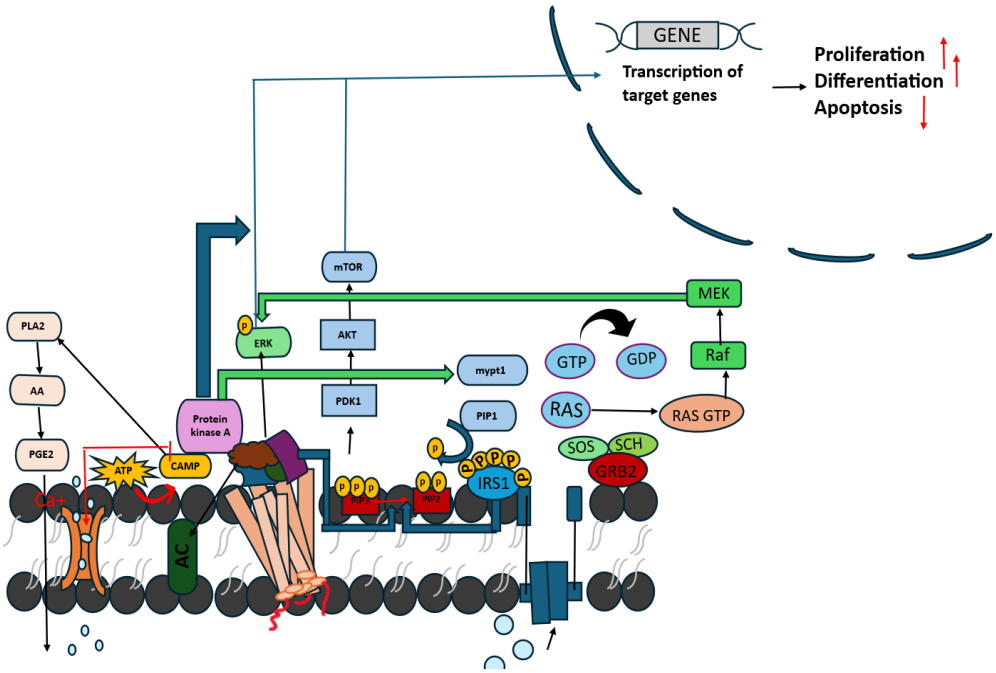

Fig 3. Integrated hormonal and growth factor signaling in Sertoli cells.

The mTOR pathway in SCs is essential for supplying nutrients to germ cells (GCs), and mTOR inhibition affects core metabolic functions in these cells (Crespo et al., 2020). Through PI3K/AKT/mTOR signaling, FSH regulates several molecules involved in cell growth and maturation, with dysregulation in this pathway linked to metabolic issues such as obesity and diabetes. Moreover, diabetes and metabolic disorders treat with GLP-1 stimulated mTOR phosphate- S2448 data also suggests that abnormal mTOR may probably be the reasons for sub-fertility and infertility in metabolic diseases (Edelsztein et al., 2016).

The IGF System:

The IGF system is, for the most part, comprised of IGF 1 and 2 together with insulin that participates in different metabolic and developmental processes. There is evidence that indicates the usage of IGF 1 receptor (IGF 1R and the control of SC proliferation by IGF-1. Notably, a connection between the IGF system and follicle-stimulating hormone (FSH) has been identified (Hart et al., 2019). When both FSHR and IGF1R are blocked, testicular weight decreases, with a more significant reduction observed in SC-Insr; Igf1r KO mice compared to SC Fshr KO mice. This suggests that IGF1 may mediate FSH-driven proliferation of immature SCs. Recent studies support this idea by showing that FSH-induced ERK1/2 and Akt phosphorylation in porcine SCs relies on an IGF1R-dependent pathway (Zaker et al., 2022).

Intriguingly, insulin can also mimic the mitogenic effects of IGF1 through binding at the site of IGF1R, despite demanding a denser concentration than the IGF1. Earlier literature has established insulin as a modulatory factor to FSH action on porcine SCs where insulin has suppressive effect on AMH and inhibin B secretion and increase in cell proliferation (Chambers & Anderson, 2015). Together, these findings indicate that the IGF system is a critical universal component of the pathways governing the endocrine and paracrine proliferation of SCs. IGF1, IGF2, and insulin as ligands of IGF1R and INSR can induce major pathways: PI3K/Akt and ERK1/2. PI3K is a kinase that controls for proteins that are required in the metabolic and proliferative features and survival of cells (Cannarella et al., 2019) (Juul & Skakkebæk, 2019).

IgF1R activation enhances the phosphorylation of IRS 1, a signaling intermediate that helps to activate several targets downstream of the insulin signaling pathway. IRS1 thus activates PI3K, which phosphorylates PIP2 to PIP3, recruiting AKT which of has multiple downstream targets many of which have an involvement in metabolism and growth. Of course, apart from PI3K/AKT it the IGF system holds pathogenetically full-spectrum impact and is proven to activate ERK 1,2 pathways (Pitetti et al., 2013) . In detail, receptor activation and IRS proteins promote Shc and Grb2 complexes, which activate Ras-GTP and activate over-components then Raf and Mek. This chain continues with the activation of the ERK protein which forms part of the processes making decisions about gene expression that affect cell proliferation. In conditions of insulin resistance, the ability of FSH to stimulate gene expression can be decreased (Crépieux et al., 2001) (Wang et al., 2018).

New data indicate that IGF1R is a part of FSH signaling: Similarly, the IGF system has reported to be proactively involved in the gonadal development in the male by densely cooperates with FSH signal transduction through, PKA activity. Typically, Insulin resistance and T2DM is characterized by heightened levels of the phosphorylated IRS-1 (Chambers & Anderson, 2015). For instance, phosphorylation of Ser 307 can suppress the signal of IRS1 interfering with the activation of both insulins early PI3K and MAPK signal cascades. That is why FSH treatments might be less effective in patients with insulin resistance, since IRS1 is one of the mediators of the FSH signaling pathway (Crespo et al., 2020).

EFFECTS OF ANDROGENS AND ESTROGENS ON SERTOLI CELLS IN OBESITY:

Notably, AR expression in SCs is absent during fetal stages in rats but progressively increases postnatally, indicating that AR's influence on SCs becomes more critical after birth. Androgens promote gene expression by binding to cytoplasmic receptors and activating pathways, including Src-mediated EGFR activation and CREB phosphorylation. This mechanism also increases cell cycle inhibitors, thereby limiting Sertoli cell (SC) proliferation in rats as the blood-testis barrier (BTB) establishes. Additionally, androgens regulate proteins like claudin-1 and claudin-5, which are vital for tight junction assembly, through interactions with the zinc transporter ZIP9 (Hazra et al., 2013).

In peritubular myoid cells (PTMCs), androgen receptor (AR) expression is present both pre- and postnatally. Androgens stimulate activin A gene expression, a paracrine factor promoting SC proliferation. Studies on transgenic mice lacking AR in PTMCs demonstrate decreased testicular weight and sperm count, likely due to reduced SC numbers. In young rats, Sertoli cells initially produce estrogens in response to follicle-stimulating hormone (FSH), but as rats mature, Leydig and germ cells (GCs) become the primary estrogen sources. Estrogens function through two receptor types, ERα and ERβ, with ERβ specifically aiding SCF expression, which supports stem cell growth and limits apoptosis. However, excessive estrogen can inhibit c-Kit expression, increase cell death, and reduce stem cell growth. G protein-coupled estrogen receptor 1 (GPER) also activates pathways that promote SC growth and survival (Rerat et al., 2022).

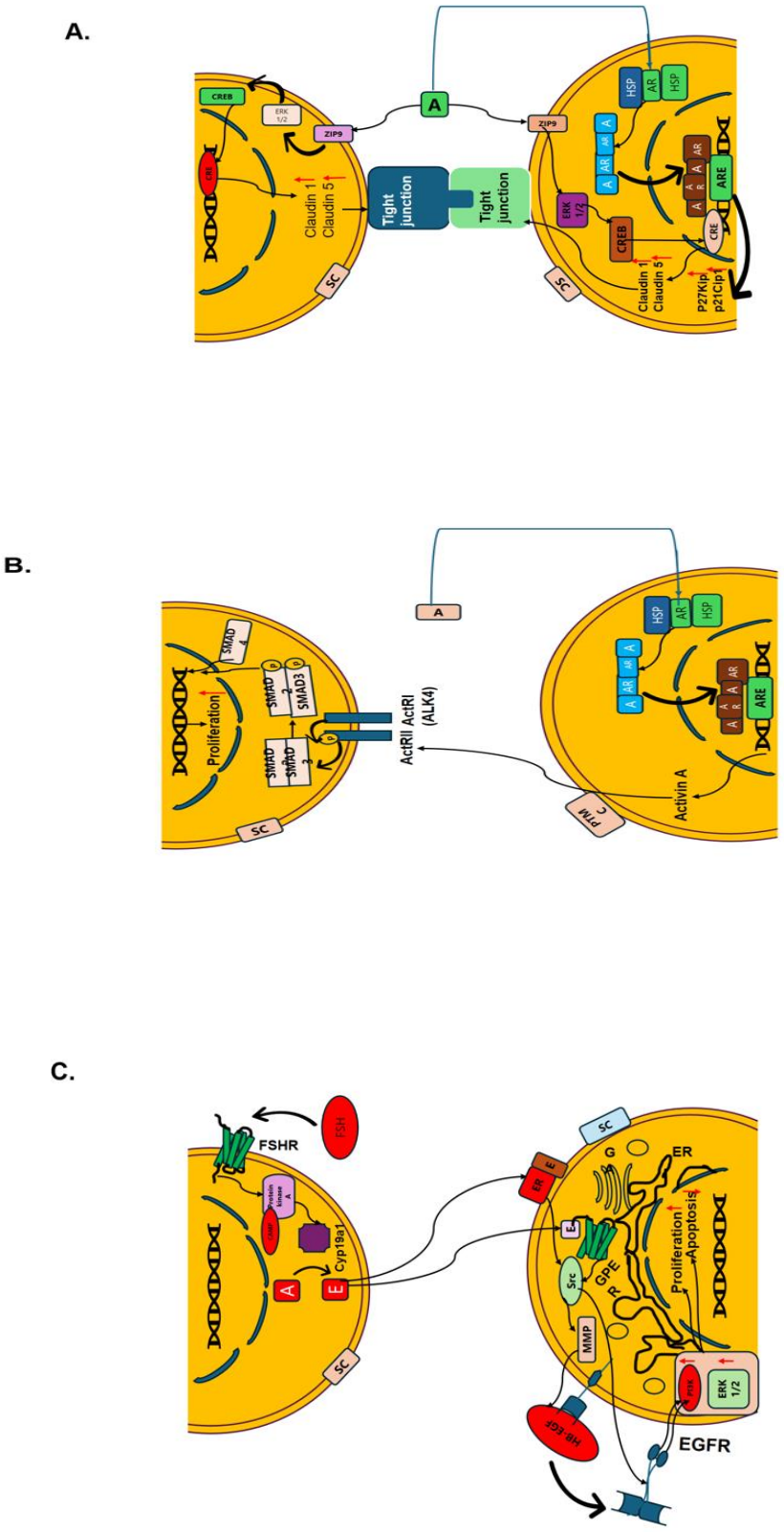

Fig. 2(A,B and C) Effect of sexual hormones on Sertoli cell differentiation, proliferation, apoptosis.

These molecular pathways are altered by obesity in SCs and lead to hormonal changes, inflammation and altered glucose metabolism, resulting in impaired male fertility. Chronic inflammation resulting from obesity may disrupt the hypothalamic–pituitary–gonadal (HPG) axis and impair the ability of Leydig cells to synthesise testosterone; in addition, SC apoptosis may be promoted (Antinozzi et al., 2021). This inflammation can also alter the PCa specific signaling cascade such as IGF1R-PI3K/AKT/mTORC pathway, which might lead to reduced testicular volume and lower AMH levels in obese children, potentially affecting sperm production later in life (Azarniad et al., 2020).

Adipocytokines further diminish SC responsiveness to FSH, limiting their capacity to produce growth factors essential for spermatogenesis. Research shows that obesity in young rats is associated with fewer Leydig cells, increased testicular macrophages, and elevated TNF-α levels, potentially reducing SC proliferation and contributing to fertility challenges in adulthood, such as oligozoospermia. This review underscores the critical balance of androgen and estrogen influences on SCs and the detrimental impact of obesity on these pathways, highlighting the importance of metabolic health for reproductive function(Barbagallo et al., 2021).

Hyperleptinima is defined as enhanced levels of leptin in serum and this is manifested commonly in obesity, and in animals fed with high fat diet (HFD) for longer duration. Leptin employed through LepR varies different signal transduction systems out of which contain JAK2/STAT, ERK, and PI3K. Leptin can reverse such effects by bringing the fertility levels back to normal in ob/ob mice that are leptin-deficient though at the same time, high levels of leptin has been link to reduced sperm concentration, agazinga, high ROS levels, low sperm steroidogenesis and impaired testicular morphogenesis (Crépieux et al., 2001) (Cannarella et al., 2023).

Leptin is integral to puberty initiation by connecting the body's energy balance with male reproductive health. Research has shown leptin's capacity to activate IRS phosphorylation in the hypothalamus, with phosphorylated IRS1 often found in insulin-resistant states, potentially disrupting the interaction between FSH and IGF1 in Sertoli cells (SCs). Further evidence indicates that leptin administration heightens hypothalamic mTOR activity, while rapamycin, an mTOR inhibitor, dampens leptin's effects (Gorczynska et al., 1994). HFDs have also been shown to decrease hypothalamic mTOR signaling, possibly contributing to leptin resistance, with mTOR also being vital in spermatogenesis and testis function. Leptin's actions on LepR in human SCs modulate acetate production and glycolysis, impacting the metabolic environment for spermatogenesis, which may link obesity with male infertility (Law & Hunzicker-Dunn, 2016).

Wang and colleagues recently reported that elevated leptin levels impair blood-testis barrier (BTB) development in young rats, reducing expression of proteins like ZO-1 and claudin 5, and downregulating androgen receptors and steroidogenic genes. This highlights hyperleptinemia's potential direct and indirect effects on SC maturation in mice (Gloaguen et al., 2011).

Hyperinsulinemia and insulin resistance, often seen in type 2 diabetes (T2DM), further impact reproductive function. In vitro studies show that insulin affects prepubertal SC function, reducing SC markers AMH and inhibin B when co-incubated with FSH. Insulin resistance, common in obese boys, might reduce SC proliferation, depleting the SC reserve. Similarly, studies observe lower inhibin B and testosterone levels during puberty in overweight boys compared to their peers, with insulin negatively impacting AMH (Lucas et al., 2014). It also described that T2DM reduces SC gene expression and expression of PI3K, Akt, and Stat3 whereas promotes FoxO1, FasL and IL-6 that can affect SC apoptosis and impaired spermatogenesis. The SC apoptosis in T2DM seems to be inhibited by the PI3K/Akt downregulation of testicular VEGF responsible for reduced testicular blood supply and therefore fertility (Martins et al., 2015).

Hypotestosteronemia and elevated estrogen levels, often seen in obesity, also impact testicular health. While physiological estrogen levels support germ

cell (GC) survival, excessive estrogen, such as in obesity, can induce GC apoptosis. Studies show that estrogens modulate proteins like Fas and Bax in testicular cells, and increase apoptosis-related enzymes, impairing antioxidant defense (Bhattacharya et al., 2019) (Brix et al., 2023).

Moreover, in vitro studies link high estrogen to glucose metabolism disruption in SCs, potentially leading to azoospermia. T deficiency also affects glucose metabolism in SCs so that nutrient support for GCs is diminished. Also, obesity causes the T levels to decrease in boy also that does not favours the development of blood-testis barrier. Both testicular and systemic androgens are crucial for maintaining genes instrumental for SCs and GC survival and noticeably lost in diabetes models leading to testicular atrophy and reduced testicular support (Holmes et al., 2021).

INTERPLAY BETWEEN GLUCOSE METABOLISM AND SERTOLI CELLS:

It has been revealed from previous studies that glucose consumption and Sertoli cell metabolism bearing an essential contribution to the growth and development of germ cells inside the testes with the help of PI3K signaling pathway. This pathway, involving mTOR and AKT, supports these metabolic processes: mTOR helptranslates amino acid to proteins whereas AKT helps glucose-transporter and phosphofructokinase in immature SCs cell metabolic growth (Wagner et al., 2016).

Outside of SCs, glucose is converted to metabolic substrates such as lactate for the development of GC through an MCT4. These process are regulated by insulin and sex hormones. The existing literature proves that SCs can regulate GLUT1 and GLUT3 according to the lack of insulin to supply lactate to GCs. Notably, insulin deficiency also decreases the concentrations of the enzymes, which encourage the synthesis of lactate from pyruvate and operate of MCT4. Further studies propose that among SCs at the IS stage, insulin levels are related to lactate synthesis (Pitetti et al., 2013).

Sex hormones such as DHT and E2 can also modulate the expression of GLUT1, GLUT3 and Pfk1; however, only DHT caused a reduction in the SCs GLUT 1 protein level and an increase in LDH activity in SCs taken from young rats. These insights suggest that obesity-related insulin resistance and hormonal imbalances can impact SC metabolism in both immature and mature stages, potentially disrupting SC function before and after puberty (Bhattacharya et al., 2019).

ROLE OF GUT HORMONES IN SERTOLI AND GERM CELL FUNCTIONALITY:

Serum of gut hormones, which play a role in appetite, satiety, lipid and carbohydrate metabolism is also affected in obesity. For instance, obese patient exhibit lower ghrelin levels when compared to their counterparts with normal body weight. Thus, as in the case of GIP, GLP-1 is also released less in obesity and type 2 diabetes (T2DM). High fat diets (HFDs) are marked to have a relationship with a rise in glucose-dependent insulinotropic enteroglucagons polypeptide also referred to as GIP that that leads to fat gain. Whereas the levels of cholecystokinin (CCK) and secretin seem to change depending on the obesity, and accordingly affect glucose metabolism. Such hormonal fluctuations could be the cause of the dysregulation of hunger cues and slower fat oxidation in obese people (Wagner et al., 2019) (Rerat et al., 2022).

Exploring how these hormones modulate Sertoli cell (SC) function may raise the possibility of how hormonal dysregulation associated with obesity contributes to infertility. For example, SCs release obesity genes like MC4R and GNPDA2 over which leptin and ghrelin act affecting the nutritional niche required for spermatogenesis. Endogenous orexigenic hormone ghrelin, regarding itself as an energy signalling molecule, modulates SC metabolism by altering GLUT levels, lactate generation and mitochondrial capacity. The body literature suggests that the ghrelins levels characteristic of obesity can decrease glucose uptake, boost pyruvate utilization, and reduce SC metabolic activity that can have an impact on spermatogenesis (Juul & Skakkebæk, 2019).

GLP-1 also regulates SCs functions and impaired glucose uptake and enhanced lactate production maybe significant for spermatogenesis stimulation. To the best of the authors' knowledge, GLP-1 has never been analysed for its ability to affect

immature SCs. The analysis of data in children revealed that obese children have increased GLP-1 levels which are connected with cardiovascular risk factors including insulin resistance and hyperglycemia. Subsequent analysis of immature SCs may offer additional support for the association of obesity in childhood with the reduction in spermatogenesis (Brix et al., 2023) (Chambers & Anderson, 2015).

Other gut hormones, including GIP and CCK, likely impact SC function, though studies are limited. Ghrelin has also been shown to protect testicular function against heat stress, a benefit that may be compromised in obese individuals with lower ghrelin levels. GLP-1 receptors in Leydig cells affect steroidogenesis, while GIP in seminal plasma suggests a role in fertility. High GIP levels in obese men support a link between nutrient intake and fertility (Brix et al., 2023).

DISCUSSION:

Numerous studies have explored the link between adult obesity and infertility; however, the effects of obesity during childhood and adolescence on future fertility are less frequently addressed but hold significant interest. Traditionally, the testis has been viewed as largely inactive until puberty, yet it undergoes substantial metabolic activity in pediatric stages. During these early years, Sertoli cells (SCs) proliferate extensively but remain immature, producing substantial amounts of Anti - Mullerian Hormone (AMH) (Edelsztein et al., 2016). As puberty approaches, SCs mature, reduce AMH production, and gain the ability to promote spermatogenesis by stimulating spermatogonia stem cells (SSCs). Each SC, however, can only support a limited number of SSCs, so any factors that hinder SC proliferation in childhood may lead to a reduced SC count, affecting SSC support and potentially resulting in irreversible oligozoospermia (Wagner et al., 2019).

Evidence indicates that metabolic conditions originating in childhood or puberty negatively impact testicular function in adulthood, often resulting in reduced testicular volume and sperm production. Obese children, for instance, tend to have lower testicular volume and AMH levels compared to healthy peers, suggesting limited SC expansion. Interestingly, delayed puberty observed in obese children has been linked to poorer sperm production in adulthood, suggesting that childhood obesity and delayed puberty may adversely impact sperm output later in life (Gloaguen et al., 2011) (Fernandez et al., 2017).

This review discusses possible mechanisms connecting childhood obesity to disrupted spermatogenesis. For example, elevated adipocytokines levels may lower FSHR and GDNF expression in immature Sertoli cells (SCs) and slow their growth, as shown in studies with young rats. Obesity-related hyperleptinemia can hinder the development of the blood-testis barrier and alter SC metabolism. Insulin, vital for SC growth, may not function properly due to insulin resistance, impairing SC proliferation. Similarly, IGF-activated receptor tyrosine kinases, which are crucial for SC growth, may also be impacted by insulin resistance, disrupting SC development. Type 2 diabetes mellitus (T2DM) further threatens SC survival by reducing testicular blood flow (Gloaguen et al., 2011).

Increased aromatization and lower SHBG levels in obese adolescents cause hyperestrogenism, which influences SC metabolism, leading to higher glucose uptake but lower lactate export—a key element for germ cell (GC) health. Low testosterone levels add to this, weakening glucose and lactate transport across the blood-testis barrier and limiting GC growth. Additionally, altered ghrelin and GLP-1 levels in obesity affect SC metabolism, reducing the energy available for GCs. Together, these metabolic disruptions create an unfavorable in the testis, potentially explaining how obesity in childhood or adolescence may harm the spermatogenic niche and contribute to infertility(Hart et al., 2019) (Lucas et al., 2014).

While evidence connecting pediatric obesity to future fertility challenges remains limited, it underscores a pressing need for further study. Long-term research on testicular growth, puberty timing, and sperm production in obese children is particularly lacking. Importantly, investigating whether weight loss can positively influence these obesity-linked issues and restore SC function is essential for lowering associated fertility risks (Martins et al., 2015) (Wang et al., 2021).

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