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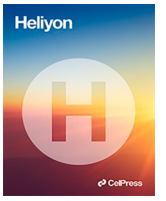

Review article

Energy metabolism and spermatogenesis

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ABSTRACT

Infertility has become a significant health burden around the globe as it is believed that 15 % of married couples struggle with infertility, with half of the problem accrued to the male. The issue of male infertility could be traced to insufficient or absence of spermatozoa. Glucose metabolism is essential for continued spermatogenesis and for the reproductive potential of sperm cells. Appropriate nutrition is critical in maintaining reproductive function as caloric restriction along with weight reduction, excessive food consumption and obesity are harmful to reproductive function. The link between metabolism and reproduction is tied to metabolic hormones like insulin, leptin and thyroid, extracellular environment, mitochondria function, nutrient substrate, availability, and environmental stressors. Although matured spermatozoa utilize glucose directly, it is not the preferred energy substrate for germ cells as they rely on Sertoli cells to supply lactate. The reproductive potential of sperm cells depends on certain modifications like hyperactivated motility, which is mainly dependent on glucose metabolism. Without other energy sources, spermatozoa utilize their internal lipid stores. The uptake and metabolism of glucose by sperm are essential endpoints for determining the potential fertility of male individuals. The biological energy in sperm cells fuels all the physiological processes they engage in, from their deposition in the female reproductive tract to the point where they fertilize an egg. This article thus reviews facts pertinent to the energy metabolism of male germ cells and Sertoli cells.

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1. Introduction

Approximately 15 % of couples face challenges in achieving pregnancy, with half of these cases attributed to male infertility. This includes conditions like low sperm count (oligozoospermia) or absence of sperm (azoospermia), often with unclear causes [1–4]. Glucose metabolism is crucial for spermatogenesis and sperm function, where sperm cells utilize glucose, fructose, and mannose for energy production via glycolysis [5,6,7]. Spermatogenesis is a complex biological process that requires significant energy expenditure to support the differentiation and maturation of sperm cells. It is well-established that disruptions in energy metabolism can have profound effects on cellular function and viability, including spermatogenesis [8]. The mitochondria, which is the powerhouse of the cell, play a critical role in providing energy for sperm motility and sperm function [9,10]. Different studies have highlighted the significance of metabolic pathways, including glycolysis and oxidative phosphorylation, in controlling male fertility [9,11–16]. Thus, determining the causes of male infertility and creating focused treatment plans require an understanding of how these metabolic processes affect spermatogenesis [9,13]. Additionally, this insight into energy metabolism and spermatogenesis has practical implications for diagnosing and treating male infertility. Conditions like varicocele and obesity, for example, are associated with metabolic dysfunction, which has been linked to impaired sperm production and quality [17]. Through the education of metabolic pathways associated with spermatogenesis, healthcare providers may thus be able to detect early indicators of infertility risk and modify treatment plans accordingly.

Sertoli cells play a vital role in spermatogenesis by producing lactate from glucose, essential for nurturing developing germ cells [18]. Hormones like FSH and insulin regulate this process. Any disruption in these processes can impair sperm motility and lead to infertility [19]. Specialized glucose transporters (GLUTs) facilitate glucose uptake into sperm cells, which is critical for their metabolic needs [20–23]. The mitochondria, on the other hand, also play a vital role in energy production and overall sperm health [21]. Mitochondria are essential for generating adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS), which is necessary for various sperm processes, including motility, capacitation, and the acrosome reaction [24]. Proper mitochondrial function is directly linked to sperm quality, and any dysfunction can lead to decreased sperm motility, concentration, and viability, ultimately contributing to male infertility [9,13].

During the process of spermatogenesis, germ cells have particular metabolic needs, and their metabolic profiles continue to evolve through the development phase [24,25]. It is not entirely obvious why this takes place; nonetheless, it is significant that testes are highly compartmentalized organs, which may limit the availability of critical molecules for the energy metabolism of germ cells. In addition to this, it has been said that the testis is an organ that is inherently devoid of oxygen [26]. All of this may help to explain why different developmental stages of germ cells need distinct metabolic pathways for the generation of energy [26,27]. Germ cells depend entirely on carbohydrate metabolism, which includes both aerobic and anaerobic processes for generating energy [28]. Spermatogonia, situated in the basal compartment of the blood-testis barrier (BTB), derive their nourishment from diverse constituents of the blood and employ glucose as an energy source to generate ATP [26]. Spermatocytes are germ cells at an intermediate stage of development that may also depend on glycolysis. Nevertheless, cells at these phases of growth have also been observed to utilize lactate, especially in cells that are located nearer to the abluminal enclosure [29]. Lactate, found in the extracellular medium and supplied by Sertoli cells, is essential for the development of mature germ cells [28,29]. However, mature germ cells express all the enzymes required in the glycolytic process.

The processes that govern the metabolism of Sertoli cells are of utmost importance to preserving spermatogenesis and male fertility. A few distinctive features characterize the breakdown of carbohydrates in Sertoli cells; For instance, the TCA cycle is solely responsible for the oxidation of 25 % of the pyruvate that is created from glucose [28]. In addition, it has been shown that cultivated Sertoli cells convert most of the glucose into lactate, which is subsequently released [21]. This process takes place after the cells have been grown. NADPH oxidation rate is one factor determining whether the pentose phosphate pathway operates at its maximum rate in Sertoli cells. It has also been observed *in vitro* that this pathway does not run at its maximal rate [28]. Lastly, in the presence of glucose, these cells can metabolize exogenous pyruvate at deficient concentrations while the glucose is present [15,21].

The majority of the lactate produced in the testes comes from Sertoli cells, and a few different factors are known to influence the synthesis of this molecule [30]. The primary source of lactate production in Sertoli cells is glucose, and the phase that slows down production the most is the transfer of glucose across the membrane from the extracellular space using GLUTs [15,31]. Research on Sertoli cells has uncovered four GLUTs, designated GLUT1, GLUT2, GLUT3, and GLUT8 [15,31]. Lactate dehydrogenase (LDH) plays a significant part in supplying lactate to develop germ cells. Research has shown that an increase in lactate supply to germ cells was caused by the export of lactate from Sertoli cells using particular monocarboxylate transporters (MCTs) [29,32,33].

As a result of genetic and epigenetic alterations of essential testicular genes, there is the potential for changes to occur in a variety of physiological processes. These processes include the disturbance of hormonal regulation, detoxification, steroidogenesis, and the proliferation and differentiation of germ cells [34]. Inexplicably, little attempt has been made to identify potential abnormalities in the energy metabolite supply for germ cells and its possible role in male gonadal disease [35]Despite the fact that these two factors may be related, this review will discuss facts pertinent to the energy metabolism of male germ cells and Sertoli cells.

2. Spermatogenesis

Spermatogenesis is the transformation of stem cells, known as spermatogonia, into specialized cells termed spermatozoa. Sertoli cells, which were first classified as cells that nourished and supported the highly developed germ cells, play a significant role in the spermatogenic process [14,36,37]. Adult spermatogenesis depends on the endocrine system's direct regulation of Sertoli cells. Sertoli cells possess the ability to proliferate and reorganize in response to endocrine regulation by luteinizing hormone/testosterone and

follicle-stimulating hormone (FSH) [26,29]. This allows these cells to create the hematotesticular barrier by forming tight junction complexes. In addition, the Sertoli cells provide nutrients and support to the germ cells. These comprise energy substrates, growth factors, and cytokines [38,39].

The testis in mammals consists primarily of highly coiled seminiferous tubules, which comprise approximately 80 % of its volume. The process of spermatogenesis occurs within these tubules [40]. The metabolic state of the testis is essential for supporting the energy demands of germ cells during the different phases of spermatogenesis, which include mitosis, meiosis, and spermiogenesis [24,41]. The remaining twenty percent of the tissue comprises Leydig cells and other interstitial components. The seminiferous tubules consist primarily of Sertoli cells (SCs), which provide a structural function. The process of spermatogenesis and male fertility heavily depends on somatic stem cells [25]. The epithelial cells are polarized and extend vertically from the basement membrane, where the peritubular myoid cells are found, towards the seminiferous tubules' lumen, which encloses the germ cells. The cells in question are located in the vicinity of the germ cells [42].

3. Metabolism and reproduction

Maintaining adequate fuel for metabolism is essential to guarantee appropriate reproductive function. Normal cellular function and survival rely greatly on glucose as a primary energy source [15,16]. Conversely, reproductive function might be negatively affected by severe conditions such as caloric restriction combined with weight loss, excessive food intake, and obesity [43]. It is increasingly estrogen receptor activity involved in maintaining the balance of energy in the body. Additionally, there is a strong connection between reproductive activity and energy metabolism [44,46,47,45]. The gonadotropin-releasing hormone (GnRH) is a highly responsive pulse generator that is affected by energy deficiency, environmental contaminants, and intense physical exertion [48]. Studies have demonstrated that brief periods of fasting can inhibit the release of GnRH pulses in males, resulting in a decrease in luteinizing hormone (LH) levels and, subsequently, testosterone levels [49–52]. This is achieved by suppressing the reproductive axis, which subsequently impacts male reproductive function. In males, a slight disturbance in energy can block the hypothalamus-pituitary-testis axis to some degree [53]. After refraining from consuming food and beverages, the concentrations of LH and testosterone decrease, but the rates at which testosterone is eliminated from the body increase [53]. Engaging in intense physical activity has been found to cause a decrease in testosterone levels by approximately 55 percent and an increase in oxidative stress in the testicles [43,54]. Disruptions to the reproductive axis will majorly impact Sertoli cell activities, as spermatogenesis depends heavily on both gonadotropic and androgen activity. Androgens and estrogens also appear to have a vital role in the treatment of metabolic illnesses [55]. Estradiol (E2) is synthesized through testosterone aromatization, which is facilitated by the aromatase enzyme complex—insufficient levels of aromatase or estrogen receptor cause insulin resistance and impaired glucose tolerance [56]. E2 is a byproduct of the conversion of testosterone that promotes insulin sensitivity in men when present at normal levels [55]. The conversion of testosterone to E2 through the activity of the estrogen receptor is essential for regulating energy balance in males [55].

There is a suggestion that the present lifestyle trends in industrialized countries have caused a rise in the occurrence of many clinical symptoms, collectively called metabolic syndrome [43]. Men who have high energy retention are more likely to develop chronic diseases. This increased risk is thought to be linked to a higher prevalence of metabolic syndrome. Enhanced energy retention promotes adipogenesis, aromatase activity, and the irreversible conversion of testosterone into E2 [39]. As a result, testosterone levels decrease, and estrogen levels increase, causing male physiology to enter a state of hypogonadal activity [57]. Hypogonadism has been associated with obesity and insulin resistance as a causative element [58]. Furthermore, decreased levels of testosterone promote the creation of oestrogen receptors, which subsequently inhibits the manifestation of GLUT4 and results in impaired regulation of glucose levels and insulin resistance [59]. A study suggested that disturbances in the molecular and cellular mechanisms of reproduction can impact Sertoli cells [29]. Sertoli cells are the focus of both follicle-stimulating hormone (FSH) and sex steroid hormones. A study also revealed that obese men with metabolic syndrome experience decreased activity in Sertoli cells, which are involved in sperm production [60,61]. This might potentially affect both sperm numbers and sperm quality. Factors such as nutritional status and the availability of energy reserves can also influence fertility [29]. Nevertheless, the precise cellular and molecular mechanisms that establish a connection between energy reserves and reproduction and the signals that facilitate these processes remain incompletely understood.

The link between metabolism and reproduction is intricately tied to the hormones that relate to metabolism and other factors like nutrient substrate and its availability [26,28,29]. Some of these hormones are insulin and thyroid hormone. Triiodothyronine causes Sertoli cells to experience membrane hyperpolarization, which stimulates the buildup of amino acids in immature rat testes [26]. The integration of reproduction and metabolism is impossible without the triiodothyronine and neuropeptides' ability to communicate with one another. Leptin, resistin, and adiponectin are the three adipokines linked with the association between energy reserves and reproductive function. Other adipokines include adipocytokine [32]. Leptin, a hormone derived from adipocytes, plays a critical role in the regulation of neuroendocrine function and fertility. It does this by stimulating the secretion of GnRH and gonadotropins (FSH and LH), as well as by restoring normal sexual function in mice that are deficient in leptin [32]. These leptin-deficient mice are sterile and unable to reproduce, but the condition may be reversed with the infusion of leptin from an external source [62]. In addition, adiponectin affects the neuroendocrine axis, which may be caused by its direct interactions with the pituitary gland [63]. At the hypothalamus-pituitary–testis axis level, these adipokines are implicated in regulating reproductive activities. They may operate via the AMPK system, which may be one of the signalling pathways that control the connections between energy balance and reproduction [23,64].

4. Glucose metabolism in sperm cells

Spermatogenesis, primarily occurring in the seminiferous tubules, is essential for sperm production and is hormonally regulated, relying on interactions among testicular cells [30,39]. Developing germ cells depend on Sertoli cells for lactate, as they cannot produce it themselves [14]. Testicular metabolism, regulated by steroid hormones, FSH, and insulin, supports germ cell survival and development [14]. Glucose is crucial for sperm hyperactivation and capacitation, vital for fertilization, with GLUTs facilitating glucose uptake [15,31]. Sperm energy metabolism adapts to environmental conditions; under anaerobic environments, sperm utilize glycolysis or fructolysis for ATP production [65]. Aerobically, sperm utilize oxidative phosphorylation via pyruvate oxidation and TCA cycle to produce ATP efficiently [66].

Glucose metabolism in sperm involves pathways like the pentose phosphate pathway (PPP), essential for sperm-egg penetration [67]. Glucose-6-phosphate dehydrogenase (G6PDH) is crucial in this pathway, regulating NADPH and pentose production vital for sperm function [68]. Understanding sperm metabolism and glucose transport dynamics is crucial for assessing male fertility and developing treatments for infertility [6,21,68]. Challenges remain in studying the effects of diseases on sperm glucose metabolism, highlighting the complexity of these processes in fertility research.

In the testes, GLUT-8 seem to be the most predominant glucose transporter, although a variety of others are also present, like the GLUT-1 to 5, and GLUT-9a and GLUT-9b. Three pivotal cells work in maintaining testicular homeostasis, amongst other functions; these cells include the Leydig cell, Sertoli cells and germ cells [15].

Leydig cells: GLUT-1, GLUT-3 and GLUT-8 transporters are found in Leydig cell membranes, and intracellular glucose transport is possible through the function of these transporters, which results in the production of ATP [15]. In testosterone biosynthesis, the rate-limiting step is ATP-dependent, which involves cholesterol transport from the cytosol to the mitochondria by the StAR protein. Therefore, the GLUT-dependent glucose homeostasis in these cells is essential for steroidogenesis [69–71].

Sertoli cells: Sertoli cells, which serve as "nurse cells" for developing germ cells and spermatozoa, are also furnished with GLUT transporters GLUT 1 to 4 [72,73]. These transporters take glucose from the interstitial fluid and convert it to pyruvate through glycolysis; pyruvate can be further metabolized along three different pathways: pyruvate dehydrogenase complex converts it to acetyl coA, alanine aminotransferase converts it to alanine, and lactate dehydrogenase (LDH) enzymatically converts pyruvate to lactate [69]. Pyruvate is an essential energy source for the continual functioning of Sertoli cells. However, lactate, which is transported to testicular germ cells via specific receptors called monocarboxylate transporters (MCTs), transforms back into pyruvate and serves as an essential source of ATP for growing germ cells [72]. Thus, GLUTs are crucial for ensuring the survival and appropriate operation of testicular cells which in turn could affect fertility [15].

Testicular cells and spermatozoa: To survive in the oxygen-depleted environment of the testes, germ cells have specific metabolic pathways for ATP production from carbohydrates. While spermatocytes and spermatids need lactate, which is supplied by Sertoli cells, glucose serves as the primary source of ATP for spermatogonia [74]. This emphasizes the importance of glucose in the process of spermatogenesis, both directly as a fuel for spermatogonia and indirectly for the other two stages of sperm formation through glucose-derived lactate [15,16]. Human spermatozoa express GLUT 1 to 3, GLUT-5 and GLUT-8. In mice, GLUT-8 is in spermatids and intra-seminiferous tubular cells with GLUT-9a and GLUT-9b. In rats, GLUT-1 and GLUT-3 are found in mature sperm, spermatids, and spermatocytes [31,69]. Because of their active glycolysis and pentose phosphate pathways, rat spermatocytes prefer pyruvate or lactate as an energy source, whereas spermatids rely on lactate because of their increased Krebs cycle activity [31]. Rat spermatozoa use fructose or glucose as energy substrates, presumably because of their low Krebs cycle activity and high glycolytic activity. Beyond

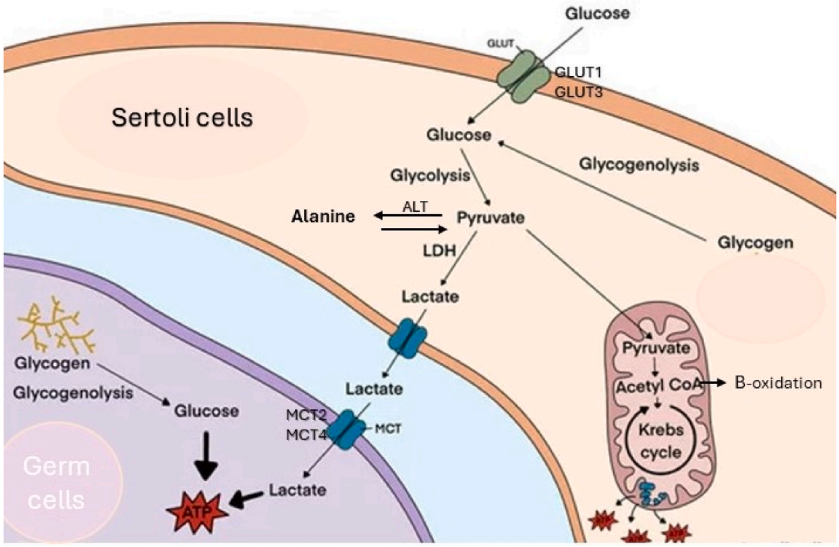

Fig. 1. Glucose metabolism in Sertoli cell and germ cell [76].

the developmental standpoint, the primary source of ATP required for capacitation and motility in mature sperm is glucose. A succession of ATP-dependent phosphorylation processes is necessary for capacitation. ATP-dependent active transport is needed to maintain the correct intracellular ionic balance for capacitation and hyperactivation (motility). This emphasizes the importance of GLUT-dependent glucose homeostasis and the critical role that ATP synthesis plays in these two functional characteristics of sperm [75].

5. The metabolic process providing energy for germ cells

The initial evidence supporting lactate as a survival factor for germ cells came from studies demonstrating that exogenous lactate stimulates RNA and protein synthesis, as well as oxygen consumption, in isolated spermatocytes and spermatids, unlike glucose [30,33,65]. These experiments underscored lactate's ability to enhance RNA and protein production in germ cells, indicating their limited reliance on glucose as an energy source when isolated. In contrast, mature spermatozoa predominantly depend on glucose for their energy needs [24].

Spermatogonia, located outside the blood-testis barrier, access energy from blood glucose, whereas more advanced germ cells like spermatocytes and spermatids reside inside, reliant on different energy sources [33]. Given the seminiferous tubules' role in maturing germ cells into sperm, ensuring varied energy sources is crucial. Spermatids possess the necessary enzymatic machinery for glycolysis, but glucose alone fails to maintain cellular ATP levels, resulting in rapid depletion when spermatids are isolated [8].

Although glycolysis is inactive in spermatids, it remains functional in spermatozoa. The mechanism by which glycolytic enzyme activity shifts from inhibition in spermatids to activation in spermatozoa remains unclear [76]. Glycolytic enzyme expression is specific to germ cells and is essential for breaking down glucose into pyruvate to fuel the Krebs cycle and oxidative phosphorylation, major ATP production processes (Fig. 1).

Despite glycolysis being a conserved metabolic process, spermatogenic cells exhibit numerous glycolytic enzymes with specific isozymes. Enzymes like hexokinase, phosphoglycerate kinase-2, and glyceraldehyde 3-phosphate dehydrogenase are encoded by unique genes expressed exclusively in spermatogenic cells [66]. Additional spermatogenic-specific glycolytic enzymes, such as phosphoglucose isomerase, aldolase, phosphoglycerate mutase, and enolase, highlight the possibility of unique genetic origins contributing to spermatogenic cell metabolism [77].

Rodents, particularly mice and rats, have been pivotal in demonstrating lactate's role in germ cell survival, stimulating RNA and protein synthesis in isolated spermatocytes and spermatids [30,33]. Human and non-human primate spermatogenic cells show similar metabolic flexibility, with spermatogonia using blood glucose and advanced germ cells utilizing lactate. Livestock species also exhibit specific glycolytic enzymes in spermatogenic cells, highlighting the conserved nature of these processes across mammals [30,33].

6. Sertoli cells: glucose transport mechanisms

Glucose transport mechanisms in Sertoli cells are critical for germ cell survival despite glucose being scarce within these cells. Glucose concentration in seminiferous tubular fluid (STF) is less than 0.02 of plasma levels, while testicular lymph holds about 75 % of plasma glucose [76]. Mature sperm metabolize external glucose, but developing germ cells rely on specialized fuels like lactate. Hexoses, essential for spermatogenesis, are transported across Sertoli cell membranes [69]. These polyhydroxylated compounds move slowly through lipid bilayers and require transporters like Sodium Dependent Glucose Transporters (SGLTs) and GLUTs. SGLTs, including SGLT1, SGLT2, and others, use sodium to transport glucose actively, whereas GLUTs like GLUT1, GLUT3, and GLUT8 facilitate passive glucose transport [76]. Sertoli cells host three known GLUT isoforms (GLUT1, GLUT3, and GLUT8), crucial for maintaining glucose homeostasis in the seminiferous epithelium. These transporters belong to three subfamilies based on tissue distribution, hexose affinity, and structural characteristics [31,69,72]. Understanding these mechanisms is vital for supporting spermatogenesis and ensuring the metabolic needs of developing germ cells are met efficiently [16,78,79]. Nevertheless, given GLUT8 has not been detected in the plasma membrane of any organs, it is unlikely to be involved in the transport of glucose from the extracellular environment [78]. Nevertheless, it is expected that not all the glucose transporters (GLUTs) discovered in stem cells (including GLUT1 and GLUT3) would equally impact transporting glucose into the cytosol. Measuring glucose absorption in males is crucial in assessing their fertility potential [76]. Therefore, it is essential to comprehend the mechanisms by which glucose is transferred from the seminiferous cord (SC), as this knowledge could potentially contribute to advancing therapies for male reproductive disorders [80].

7. The critical role of Sertoli cell metabolism in germ development

The production of germ cells is a highly organized and precisely timed process, primarily controlled by stem cells. Indeed, each somatic cell (SC) possesses a specific capacity to support a certain number of germ cells, although this capacity differs among different species. The testis of an adult rat has a Sertoli cell-to-germ cell ratio of approximately 1:50 [81]. The quantity of somatic cells in an individual directly affects the capacity to sustain germ cells through spermatogenesis, thereby impacting the daily production of sperm. This ingredient exerts an influence on fertility [39]. Mature stem cells develop a specific spatial organization, enabling them to interact both morphologically and chemically with different generations of germ cells, peritubular myoid cells, and Leydig cells responsible for steroid production [39]. Adult stem cells can fulfil a significant function inside the reproductive system. The bottom part of the SC is in direct contact with spermatogonia [82]. The sides of the SC send out extensions around spermatocytes and early spermatids. The top part of the SC is closely connected to elongating and elongated spermatids and faces the inner part of the tubule where sperm is released [82].

The migration of germ cells through the blood-testis barrier (BTB) is a tightly regulated process involving periodic disintegration and reassembly of junctional complexes. This allows germ cells to pass while maintaining BTB integrity [23]. Initiation of meiosis prompts germ cells outside the BTB to cross it, relying on supporting cells for sustenance. Premature BTB transit results in immature sperm, impairing fertility; hindrance causes germ cell removal via phagocytosis, inevitably leading to infertility. Stem cells (SCs) metabolize diverse substances, primarily glucose, via glycolysis [66]. Glucose enters cells and undergoes glycolysis, producing ATP, pyruvate, and NADH. Irreversible enzyme-regulated steps include hexokinase, phosphofructokinase, and pyruvate kinase. In hypoxia, glycolysis yields lactic acid via LDH action. LDHC, expressed uniquely in germ cells, plays a pivotal role in their metabolism [66]. Lactate, a preferred ATP substrate, crosses membranes via monocarboxylate transporters (MCTs), crucial for spermatogenesis, enhancing outcomes in cryptorchidism [30,33,65]. Glucose deficiency reduces fertilization; it's vital for hyperactivated sperm motility and capacitation pathways. Glycogen's role in SCs and its impact on spermatogenesis, particularly under glucose transport deficiency, are subjects of study. SCs' glycogen metabolism and potential adaptive roles in adverse metabolic conditions indicate their pivotal function in lactate production [21,74]. Spermatogonial stem cells (SCs) within seminiferous tubules create an environment crucial for germ cell development into spermatozoa. SCs ensure germ cells receive adequate energy substrates, failure triggers apoptosis. Glucose metabolism in SCs generates growth and regulatory factors vital for germ cell development. Controlled glucose metabolism in Sertoli cells is essential for efficient sperm production [33].

8. Implications of deregulation in glucose transport and metabolism in Sertoli cells

As previously mentioned, a crucial role of SC is to facilitate the transportation and metabolic processing of glucose, resulting in the production of lactate for the growth and development of germ cells [33,36,39]. Any dysregulation that affects these systems is likely to undermine the energy supply to germ cells and, as a result, reduce male fertility [83]. Glucose transport across the cell membrane is a crucial step in lactate formation. The hypothesis that glucose can regulate its transport and metabolism was derived from research conducted on cultured mammalian cells, which showed enhanced rates of glucose uptake in response to glucose deprivation [6]. Despite the similarities in sequence, glucose transporter (GLUT) isoforms differ in their regulation and tissue distribution. Deprivation of glucose has been shown to enhance GLUT1 and GLUT3 levels via AMP-activated protein kinase (AMPK), PI3K/PKB, and p38 MAPK pathways. FSH, insulin, growth factors, and cytokines also influence GLUT1 and GLUT3 expression distinctly [31,69,72]. These factors signal stem cells to adjust glucose transporter activity, ensuring adequate lactate production critical for germ cell development. IGF-1, akin to insulin, modulates glucose transport through IRS interactions. Dysregulation in spinal cord glucose transport and metabolism can impair male fertility. Stem cells employ compensatory mechanisms to meet germ cell energy demands under adverse conditions. Understanding the role of IGF-1 in glucose uptake by stem cells is crucial [33]. Further research is needed to explore the implications of glucose dysregulation in stem cell metabolism and fertility issues.

9. Role of pyruvate and lactate in sperm capacitation

Pyruvate and lactate are often employed as energy substrates by mammalian spermatozoa because they are found in large concentrations in oviductal fluid and glucose. As a result of this, glucose is not the sole energy source in this fluid [84]. In addition, the metabolism of pyruvate is closely linked to the metabolism of lactate, which results from the enzymatic reduction of pyruvate that is carried out by lactate dehydrogenase [85]. This process, particularly under anaerobic circumstances, is responsible for the regeneration of cytosolic NAD^+, which is essential to the progression of glycolysis. In addition, the mitochondrial lactate transporter may transfer lactate from the cytosol into the mitochondria of sperm cells, where it can then undergo further metabolic processes [85]. Sperm mitochondria contain a unique lactate dehydrogenase variant, LDH-X or LDH-C4, which converts lactate back to pyruvate within the mitochondrial matrix [86]. This variant is exclusive to sperm mitochondria, although LDH-X is more commonly found in the cytosol. The combined activities of cytosolic and mitochondrial LDH, along with the lactate carrier, facilitate glycolysis for NAD^+ production and transport reducing equivalents for OXPHOS [87].

Pyruvate has been found to speed up glycolysis and improve the ability of human spermatozoa to undergo capacitation. Exogenous pyruvate can speed up glycolysis by helping convert pyruvate to lactate through LDH while replenishing cytosolic NAD^+ [84]. Specifically, the researchers discovered that when metabolic substrates were not present, the levels of endogenous ATP decreased when mitochondrial respiration inhibitors, such as antimycin A, rotenone, and NaCN, were introduced [84]. The finding indicated that exogenous pyruvate enhances ATP synthesis independently of mitochondrial respiration by restoring NAD^+ after conversion to lactate [84].

10. Sperm motility and flagellar movements

The motility machinery of a spermatozoon is housed in the sperm flagellum, which assists the spermatozoon in its forward motion until it can enter an egg [88]. The bending of the flagellum, which is necessary for "flagellar motions," makes possible microtubule movements, particularly the "arms" of the dynein protein that are found in eukaryotic flagella [89].

The axonemal protein known as dynein is responsible for the regular flagella beat. The bending of the flagellum results from the activation of dynein ATPases, which in turn causes the externally located axonemal doublet microtubules to move [88,89]. Therefore, dynein generates the force needed for flagellar movement by converting the chemical energy from ATP hydrolysis into the required mechanical energy [90].

Due to their dense nature, mitochondria are in the central region of the sperm cell rather than the flagellum. This positioning helps

avoid mechanical constraints that could impede the flagellum's motion [91]. The ETC efficiently facilitates the generation of ATP. However, it remains uncertain whether the ATP produced by mitochondria is capable of adequately diffusing across the entire length of the spermatozoa flagellum to meet the energy demands of flagellar beating [91]. Biophysicists found ATP diffusion from the midpiece to the flagellum in bulls and sea urchins sufficient for proper flagellar beating. The concept of sperm motility being assessed by mitochondrial membrane potential was elucidated and showed a drop in this potential results in reduced sperm motility and impaired ability to fertilize eggs [8]. Asthenozoospermic patients show a link between nonlinear sperm motility and mitochondrial membrane function. Changes in the mitochondrial respiratory chain, including its complexes and electron carriers, affect sperm motility and ATP production [92]. Therefore, it has been postulated that alterations in these constituents are responsible for idiopathic asthenozoospermia [66].

In addition, sperm cells have several different carbohydrate alternatives to produce ATP, which they may employ as a substrate [90]. This helps to explain why some people believe that the flagellum can produce the ATP necessary for its movement, irrespective of the action of the mitochondria [91]. Glucose causes an increase in the frequency of flagellar beating and is the most essential substrate for the creation of ATP [90]. In a research, a glucose analogue known as 2-deoxyglucose—DOG was used to obstruct the glycolysis process in spermatozoa. DOG inhibited the activities of pyruvate and lactate without impacting mitochondrial respiration [93]. This demonstrated that inhibiting glycolysis decreased ATP content and sperm motility, highlighting glycolysis as crucial for sperm energy [93]. Despite DOG not affecting mitochondrial ATP production, ATP levels remained unchanged, indicating mitochondrial respiration alone is insufficient for sperm motility. These findings support glycolysis as the primary energy source for sperm motility [93]. Key enzymes like GAPD, necessary for glycolysis, are linked to the sperm flagellum's fibrous sheath. GAPD, critical in spermatogenesis, is sensitive to environmental factors affecting male fertility. The GAPD-S gene is present in spermatogenic cells in mice, whereas humans have the GAPD-2 gene [33].

11. Mechanisms of sperm activation and fertilization: role of ATP and molecular processes

Sperm fertilization involves capacitation, hyperactivation, and acrosome reaction phases. It precedes effective fertilization [94]. About 10–20 % of sperm showed hyperactivation-like motility after capacitation, dependent on an ample ATP supply [8]. Capacitation of spermatozoa induces alterations in both the surface of the sperm head and the length of the flagella [95]. Extra energy activates sperm, initiating the acrosome reaction. This releases hydrolytic enzymes, facilitating sperm binding and oocyte penetration. Egg signals activate G-proteins, elevating Ca^{2+} levels, and triggering kinases and protein phosphorylation, which are essential for successful fertilization [96]. A vital Ca^{2+} ion reservoir may be located adjacent to the base of the mitochondrial sheath in the sperm midpiece. This storage is located within the excessive nuclear envelope comprising aggregated membrane vesicles. The elevation of Ca^{2+} levels in spermatozoa, triggered by acrosome reaction stimuli, enhances the intensity of sperm flagellar beating, resulting in a heightened degree of hyperactivation [97]. Given that ATPase activity, cyclic adenosine monophosphate production, and phosphorylation all require adenosine triphosphate (ATP), it may be concluded that ATP is crucial for maintaining the structural integrity of the acrosome and triggering the acrosome response (Fig. 2). Mitochondria play a vital role in enabling tyrosine phosphorylation in capacitated sperm [98]. The Ca^{2+}-ATPase-aided secretory pathway in the spermatozoa midpiece may be responsible for removing excessive intracellular Ca^{2+} that has been released from the surplus nuclear envelope [96]. Furthermore, the testes after puberty include a significantly greater number of spermatids that exhibit a substantial level of the selenium-dependent phospholipid hydroperoxide glutathione peroxidase [96]. This gene is only expressed in the midpiece region of fully developed spermatozoa. It is involved in both the functioning of mitochondria and the maturation process of sperm. The mitochondrial helix is in this specific area [99]. While the statement above provides valuable insights into the molecular mechanisms underlying sperm activation and the acrosome reaction, several gaps in knowledge remain. For instance, the precise role of ATP in maintaining the structural integrity of the acrosome and triggering the acrosome response warrants further investigation. Understanding how ATP influences critical processes such as tyrosine phosphorylation and cyclic adenosine monophosphate production during sperm capacitation is crucial for unravelling the intricacies of fertilization.

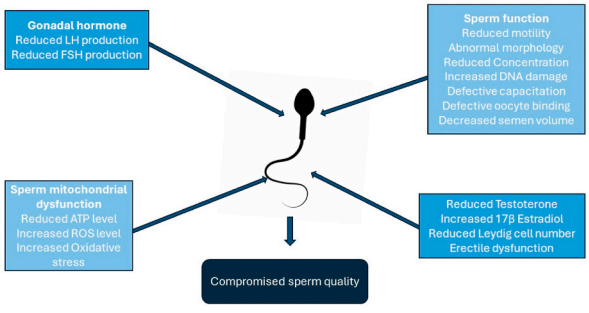

Fig. 2. Major effects of energy imbalance affecting steroidogenesis and spermatogenesis.

12. Energy depletion in sperm: implications

Adequate ATP in sperm cells is required for everyday functions. Research has demonstrated that a significant decrease in ATP levels can rapidly reduce the frequency of flagellar beats, as seen in fish sperm, where the beat frequency dropped from around 60 to 20 Hz within just 20 s [100]. As ATP was gradually depleted, the frequency of movements and ATP concentration decreased steadily. This supports the idea that the activation of the axonemal machinery, potentially involving dynein-ATPase, is linked to calcium ion-dependent cAMP regulation [100]. This is further supported by observations showing that sperm do not entirely exhaust their ATP content, and their ATPase activities are lower during the recovery phase than the motility phase (Fig. 2). Moreover, sperm that have restored ATP levels, like quiescent sperm, are unable to swim or hydrolyze ATP for energy unless there is once again a sufficient external source of calcium ions [89,101]. It has been suggested that the gradual depletion of ATP in fish sperm, caused by axonemal motion, may affect flagellar morphology, potentially stiffening the distal region of the flagellum [89,101]. This stiffening could result from ATP depletion in the distal flagellar region, which is distant from the site of mitochondrial ATP generation. Consequently, this may lead to dynein blockage, inducing rigidity in the flagellum. Such changes, coupled with fluctuations in intracellular ion concentrations, directly affect dynein activity [102,103].

However, despite these insights, several gaps in knowledge remain. For instance, while the role of calcium ions in axonemal machinery activation is highlighted, the precise mechanisms underlying this process, particularly the involvement of dynein-ATPase and cAMP regulation, warrant further investigation [100].

Moreover, the observed phenomenon of sperm not completely depleting their ATP content raises questions about the mechanisms governing ATP utilization and replenishment during sperm motility and recovery. Additionally, the potential impact of ATP depletion on flagellar morphology, particularly the stiffening of the distal flagellar region, presents an intriguing avenue for future research [99]. Understanding the interplay between ATP depletion, flagellar morphology alterations, and dynein activity fluctuations could provide valuable insights into the mechanisms governing sperm motility and function.

13. Future perspectives

As research continues to uncover the complexities of energy metabolism with male reproductive wellness, there is potential for identifying novel therapeutic targets. These targets could lead to interventions to improve mitochondrial health, thereby enhancing sperm quality and fertility outcomes. Additionally, the role of lifestyle factors, such as diet, exercise, and environmental exposures, in modulating energy metabolism and spermatogenesis will likely gain more attention [43]. Understanding how these factors influence mitochondrial function and overall reproductive health could inform public health strategies and individual lifestyle modifications to mitigate risks associated with male infertility [10]. Furthermore, advancements in reproductive technologies and personalized medicine may allow for tailored approaches to address metabolic disorders that impact spermatogenesis. Overall, a multidisciplinary approach integrating molecular biology, endocrinology, and environmental health will be essential for advancing our knowledge of energy metabolism's role in spermatogenesis and improving male reproductive health.

14. Conclusion

The conclusion drawn from the review emphasizes the critical role of metabolism in reproductive processes, particularly focusing on sperm development and function, as well as the metabolic support provided by Sertoli cells. Disruptions in glucose transport and metabolism in Sertoli cells can profoundly affect male fertility by compromising the energy supply to germ cells. Understanding the molecular mechanisms involved in glucose transport regulation is essential for addressing fertility issues associated with metabolic dysregulation in Sertoli cells. Furthermore, energy substrates like pyruvate and lactate play integral roles in sperm physiology, contributing to glycolysis and oxidative phosphorylation. The source of ATP for sperm flagellar movements remains debated, highlighting the complexity of sperm physiology and the need for further research. The metabolic processes in glucose utilization are crucial for supporting germ cell development and function in the testis. Glucose transport mechanisms and glycogen storage in Sertoli cells ensure efficient energy supply, underscoring the importance of metabolic collaboration within the testis.

The intricate relationship between metabolism and reproduction extends beyond hormonal regulation to include adipokines, emphasizing the interconnectedness of energy balance and reproductive health. Understanding these processes is essential for addressing male infertility and gonadal diseases, with potential implications for novel therapeutic strategies. Despite advancements in understanding sperm energetics, many questions remain unanswered, highlighting the need for further research to enhance *in vitro* storage mediums and develop effective contraception methods. Overall, elucidating the complex interplay between metabolism and reproduction is crucial for advancing fertility research and improving clinical outcomes for individuals experiencing fertility challenges.

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CRediT authorship contribution statement

Damilare Emmanuel Rotimi: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Matthew Iyobhebhe:** Writing – review & editing, Writing – original draft, Resources, Data curation, Conceptualization. **Elizabeth Temidayo Oluwayemi:** Writing – review & editing, Writing – original draft, Resources, Data curation, Conceptualization. **Olasunkanmi Peter Olajide:** Writing – review & editing, Writing – original draft, Resources, Data curation, Conceptualization. **Bolanle Adenike Akinsanola:** Writing – review & editing, Writing – original draft, Resources, Data curation, Conceptualization. **Ikponmwosa Owen Evbuomwan:** Writing – review & editing, Writing – original draft, Resources, Data curation, Conceptualization. **Rotdelmwa Maimako Asaleye:** Writing – review & editing, Writing – original draft, Resources, Data curation, Conceptualization. **Oluwafemi Adeleke Ojo:** Writing – review & editing, Writing – original draft, Resources, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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