International Journal of Diabetology & Vascular Disease Research (IJDVR)
ISSN:2328-353X

The Burden of Metabolic Diseases on Male Reproductive Health

Editorial

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During the recent decades, we have witnessed fertility rates dwindling worldwide, while metabolic diseases followed an opposite tendency, with their prevalence dramatically increasing [1-3]. Those trends are particularly marked in both developed and under-development countries, where type 2 diabetes mellitus (T2DM) and obesity are key players in the ever-increasingly number of new metabolic disorder cases, fostered by overeating and sedentarism [3, 4].

The previous premises, acting during the same time period, arose the possibility of metabolic disorders and infertility were somehow connected. In addition, a normal reproductive function requires a significant quantity of energy, so it is highly influenced by energy homeostasis [5, 6]. Furthermore, the prevalence of reproductive dysfunction is significantly higher in people suffering from metabolic diseases, particularly males. From all the infertility cases documented worldwide, about a third account for male-only factor. In fact, even a pre-diabetic state is enough to harm sperm parameters [7]. However, the mechanisms underlying this link are still controversial.

The most evident burdens of metabolic diseases on male reproductive function are caused by complications on other systems. Obese men experience more cases of erectile dysfunction than lean males, due to cardiovascular co-morbidities. They can also suffer coitus difficulties due to excessive pubic fat deposition, which leads to other reproductive health risks, such as scrotal heating, responsible for defects in spermatogenesis. T2DM patients are also prone to erectile dysfunction and scrotal heating due to vascular disease [8]. Nevertheless, the most severe and persistent effects of metabolic disorders on male reproductive function are linked to hormonal impairment.

The steroidogenic potential of adipocytes is a good example of how a metabolic disorder, in this case obesity, is able to induce hormonal problems, and consequently affect reproductive function. Adipocytes have intense p450 aromatase, an enzyme responsible to convert testosterone into 17β-oestradiol (E_2). Thus, obese men present higher E_2 bloodstream concentration and lower testosterone than lean men. This action results in two immediate negative effects for male fertility: 1) Testosterone depletion leads men towards an hypogonadal state, and 2) E_2 secretion may exert negative feedback over pituitary gland and thus disrupt the reproductive axis. The former, inhibits the release of Gonadotrophin-Releasing Hormone (GnRH) and, consequently, of the gonadotrophins Follicle Stimulatory-Hormone (FSH) and Luteinizing Hormone (LH). LH stimulates testosterone release from Leydig Cells, so ultimately reproductive axis disruption leads to the formerly mentioned lower testosterone concentration. Sertoli cells are crucial for spermatogenesis because they establish the blood-testis barrier (BTB), one of the tightest blood-barriers of our body [8]. Testosterone (and their precursors) and FSH direct Sertoli cell metabolism towards a glycolytic profile, uptaking more glucose, increasing lactate dehydrogenase (LDH) efficiency and releasing more lactate and acetate into the seminiferous tubule's adluminal space [9, 10]. Lactate is one of the preferential substrates for germ cell energy sources, besides presenting anti-apoptotic effects on these germ line cells [11]. Oestrogens also play an important role on seminiferous tubular fluid composition and pH control, as they regulate the expression of several ionic transporters in Sertoli cells [12-14]. Globally, oestrogens diminish transcellular transport rate and increases Sertoli cell's intracellular pH [12].

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Received: March 01, 2017
Published: March 04, 2017

Citation: Crisóstomo L, Sousa M, Alves MG, Oliveira PF (2017) The Burden of Metabolic Diseases on Male Reproductive Health. *Int J Diabetol Vasc Dis Res*,. 5(1e), 1-2.
doi: http://dx.doi.org/10.19070/2328-353X-1700012e

Unsurprisingly, gut hormones are major players linking metabolic disorders and reproductive function. Insulin is produced and released by pancreatic β-cells in response to high serum glucose concentration, and promotes global glucose uptake and metabolism. Testicular cells are not an exception. Insulin also promotes the expression of glucose transporter family members (GLUT), the glycolytic metabolism and lactate production by Sertoli cells. In addition, type 1 diabetes mellitus (T1DM) patients present lower expression of enzymes linked to glycolysis and GLUTs in testis, and lower lactate concentration in the adluminal compartment [15]. There is also *in vitro* evidence that those effects are present in Sertoli cells and directly connected to insulin deprivation [16].

Ghrelin is mainly secreted by the stomach in response to satiety. Its serum levels are inversely proportional to the global nutritional state. Ghrelin acts as a nutritional sensor for the pulsatile GnRH release by hypothalamus. Since reproductive function requires proper nutritional support [17] it is expected that ghrelin may be important for male reproductive health. Extremely low (obesity) and high (undernutrition) values of ghrelin inhibit GnRH pulses, disrupting the hypothalamus-pituitary-reproductive axis [5, 18] also suggesting a major role in male reproductive physiology. Ghrelin is capable of inhibiting testicular steroidogenesis by downregulation of upstream elements of the steroidogenic pathway [5]. These effects are quite similar to those of leptin, and the ghrelin-leptin axis is pictured as a mechanism to avoid overeating [5]. Ghrelin also regulates insulin resistance in a dose-dependent manner [17]. Higher ghrelin concentration is associated to higher insulin resistance, which is correlated to Sertoli cell metabolic shift towards glycogenesis [19, 20], in detriment of glycolysis and lactate production for germ cells. That may result in spermatogenesis arrest.

Leptin is another hormone linked to satiety, although it is mainly expressed by adipocytes. Therefore, a higher adipose tissue mass means higher leptin blood concentration, and obesity is associated to the highest values. GLUT expression is upregulated by lean-like leptin concentrations in Sertoli cells, but not by obese-like concentrations, although in both conditions acetate production was inhibited and LDH activity increased [21]. This data suggests a metabolic reroute towards β-oxidation using fatty acids as preferred substrate. Notably, leptin is known to inhibit testicular steroidogenesis by inhibiting the expression of enzymes needed for the transport and the conversion of cholesterol into steroids [5].

The burden of metabolic disorders on male reproductive function is already being extensively characterized in bibliography. Nonetheless, there is still a significant number of factors that are poorly or not described at all. This subject has tremendous research potential and knowledge about it is urgently needed, in order to tackle the pandemic in infertility, by understanding some of its causes, and particularly associated with metabolic disorders, by describing the whole consequences of them.

Acknowledgements

This work was supported by the Portuguese Foundation for Science and Technology: M.G. Alves (IFCT2015 and PTDC/BIM-MET/4712/2014); P.F. Oliveira (IFCT2015 and PTDC/BBB-BQB/1368/2014); and UMIB (Pest-OE/SAU/UI0215/2014); co-funded by FEDER funds through the POCI/COMPETE 2020.

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