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Impairment of male fertility – a consequential problem of our time. The impact of obesity and related metabolic disorders

Zaburzenia płodności u mężczyzn – ważki problem naszych czasów. Wpływ otyłości i związanych z nią zaburzeń metabolicznych

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Słowa kluczowe

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Summary

Infertility, one of the consequential problems of our time in a great percentage affects men. Among the many factors which are taken into account as the causes of this phenomenon some are attributable to obesity and related metabolic disorders. Quite a few mechanisms by which excess body weight and related diseases (type 2 diabetes, dyslipidaemia) negatively affect the men ability to reproduction, both spontaneous and assisted, are considered. In this review the impact of obesity and type 2 diabetes on the hormonal control of spermatogenesis and the direct effects of these factors on the process of sperm production are discussed. Also the observed result – the progressive deterioration of the semen quality and damage to the genetic material (DNA) of germ cells are elaborated. Moreover, unfavorable role of obesity and diabetes in the development of vascular lesions, resulting in a various degree erectile dysfunctions is briefly presented. Higher body mass index (BMI), insulin resistance and diabetes also affect adversely the inheritance process. In a consequence a decreased reproductive ability in the second and even third generation descendants of the obese fathers is observed.

Understanding the impact of obesity – a real epidemic of the 21st century on fertility is of crucial importance for undertaking effective counteracts to this disturbing phenomena.

Streszczenie

Niepłodność, jeden z problemów naszych czasów o narastającym znaczeniu, w dużym odsetku przypadków dotyka także mężczyzn. Wśród wielu czynników branych pod uwagę jako przyczyny tego zjawiska ważna rola przypada otyłości i związanym z nią zaburzeniom metabolicznym. Rozpatruje się wiele mechanizmów, poprzez które nadmierna masa ciała i związane z nią choroby (cukrzyca typu 2, dyslipidemia) negatywnie wpływają na zdolność mężczyzn do rozrodu, zarówno spontanicznego, jak i wspomaganego. W pracy omówiony jest wpływ otyłości i cukrzycy typu 2 na kontrolę hormonalną spermatogenezy oraz bezpośrednie działanie tych czynników na proces produkcji plemników, w wyniku czego u mężczyzn dochodzi do postępującego pogarszania się jakości nasienia i uszkodzenia materiału genetycznego (DNA) komórek zarodkowych. Wskazuje się także na niekorzystną rolę otyłości i cukrzycy przyczyniających się do rozwoju zmian naczyniowych, czego efektem są zaburzenia potencji. Podwyższony wskaźnik masy ciała (BMI), insulinooporność i cukrzyca wpływają także niekorzystnie na procesy dziedziczenia, czego skutkiem jest zmniejszenie możliwości reprodukcyjnych w drugim, a nawet trzecim pokoleniu potomków ojców otyłych.

Rozumienie wpływu otyłości – prawdziwej epidemii XXI wieku, na płodność jest podstawowym warunkiem podjęcia skutecznego przeciwdziała tym niepokojącym zjawiskom.

Conflict of interest
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INTRODUCTION AND EPIDEMIOLOGY

Impairment of fertility is a great problem of couples nowadays. It is estimated that even 15% of people in the reproductive age in the developed countries may be infertile (1). Epidemiological and clinical data show that every seventh couple in the Western world is infertile currently, and in 40% it results from a "problem" of the man (2). For example, it has been shown in the USA that fertility rates (births per 1000 men) decreased from 57.0 in 1980 to 45.8 in 2013 (3). Similar data comes from Europe. It was found in Denmark that the number of newborns per man at the 45 years of age declined in years 1990-2005 from 1.9 to 1.7 (4).

Sub- or total infertility is a result of several genetic and non-genetic factors. As it has been observed in the numerous cohort studies, one of the more important among these factors is obesity. Data from The Danish National Birth Cohort Study, published in the 2007 year obtained on the basis of the analysis of 47 835 pairs showed that the time to pregnancy (TTP) over 12 months happens much more often when the men has a body mass index (BMI) over 30 kg/m^2 compared to men without obesity: AOR (adjusted odds ratio) for obesity in men is 1.53 (95% CI 1.32-1.77). If excessive weight occurs either in female the AOR rises to 2.75 (95% CI 2.27-3.30) (5). Also The Norwegian Mother and Child Cohort Study, involving 26 303 couples has shown that TTP longer than 12 months is observed more often when a man is overweight (BMI > 27 kg/m^2). AOR in such situation is 1.20 (1.04-1.38). When a man's BMI rises above 30 kg/m^2 AOR increases to 1.36 (1.13-1.63) (6). The impact of obesity on fertility must be therefore regarded as an important social problem, especially when it is well known that since 1980 the number of obese people all over the world has doubled and now 65% of people live in countries in which excessive body weight is a larger health problem than malnutrition. It is calculated that the health costs of obesity in developed countries reaches approximately £ 2 billion per year (7). Concomitantly, in the last 50 years a continuous decline in fertility has been observed, parallel to the growth of the degree of obesity (8). Male infertility is largely associated with the deterioration of the semen quality. A direct correlation between BMI and a decline in the number and motility of sperm was proved (9). Already overweight, and to a greater extent obesity increase the risk of damage of germ cell's DNA (10). Moreover, it is well known that excessive body weight affects the sexual possibilities. Erectile dysfunction of a various degree have been found nearly in 96% of the 256 men with metabolic syndrome (11).

MECHANISMS OF OBESITY-RELATED MALE FERTILITY IMPAIRMENT

Considering the factors contributing to the deterioration of fertility in obese men it should be mentioned (fig. 1):

- hypogonadotropic hypogonadism,
- increased aromatization of testosterone to estrogens,
- low sex hormone binding globulin (SHBG) serum levels,
- the deterioration of the quality of semen: reduction of the number of sperm and damage of their DNA,
- peripheral vascular disease leading to erectile dysfunction,
- remote impact of first and perhaps even second generation ancestors obesity (12, 13).

IMPACT OF OBESITY ON THE HORMONAL REGULATION OF REPRODUCTION PROCESSES IN MEN

Spermatogenesis and sexual ability in men are strictly regulated by the hypothalamic-pituitary-gonadal axis

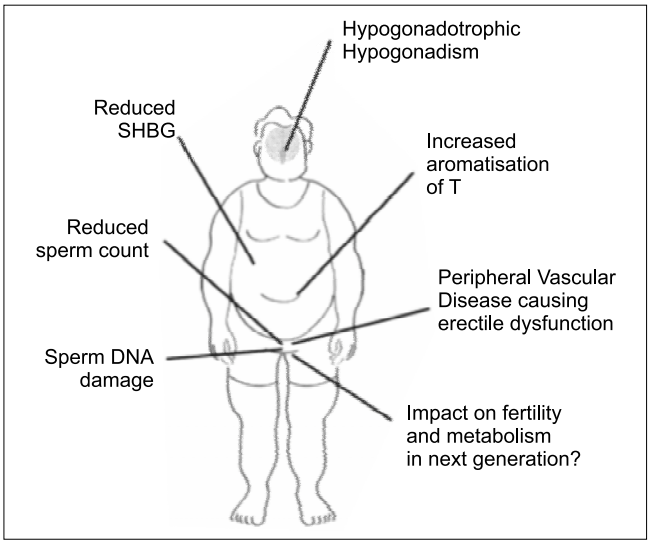

Fig. 1. Factors associated with obesity that affect male fertility (according to (12))

hormones. In obesity which can be treated as a chronic inflammation state this control is disturbed. Excessively expanded and functionally changed adipose tissue becomes a source of many cytokines (adipokines). Some of them, i.e. tumor necrosis factor alpha (TNFα), interleukin 6 (Il-6) as well as several other factors inhibit the production of kisspeptin, a key protein in the mechanism of gonadotropin-releasing hormone (GnRH) secretion in the hypothalamus (14). This effect of adipokines activity is exacerbated by the estrogens. Higher levels of these hormones is a result of the increased aromatization from androgens in large amounts of fat tissue. It has been proved that estrogens, especially in low SHBG conditions actively inhibit the expression of kisspeptin (10). Leptin is an another factor contributing to low kisspeptin production. Although physiologically leptin stimulates GnRH secretion, in case of obesity leptin resistance develops with subsequent inhibition of gonadotropin-releasing hormone synthesis (15). It seems, that kisspeptin expression can be considered as the process that integrates the impact of obesity, testosterone deficiency and the effects of external factors on the hypothalamic-pituitary-gonadal axis. The corollary of the incorrect GnRH secretion is the hypogonadotropic hypogonadism with subsequent testosterone deficiency. In addition, there is a peripheral mechanism that contributes to low testosterone production. This mechanism is again associated with leptin, which blocks the effect of luteinizing hormone (LH) on the Leydig cells and on this way enhancing deficit of androgens (15). In turn, the reduction in the follicle stimulating hormone (FSH) secretion leads to decline in production of inhibin B in Sertoli cells. Inhibin B in normal state stimulates Leydig cells to testosterone secretion and is considered as an indicator of normal spermatogenesis. Its deficiency in obesity may be used as a marker of dysfunction of the seminiferous tubules and reduced number of Sertoli cells.

IMPACT OF OBESITY ON SPERM QUALITY

Male infertility is finally a result of abnormal spermatogenesis. The formation of sperm cells in the seminiferous tubules is a complex process regulated in auto-, para-, and endocrine manner. The key hormone in this process is testosterone, which affects the Sertoli and the epithelial cells of the seminiferous tubules. The Sertoli cells provide nutrients and support, being the only somatic cells in direct contact with developing germ cells. They also produce androgen-binding protein (ABP), which contributes towards a higher concentration of testosterone in testes. Moreover, the Sertoli cells secrete many other active biological substances, such as growth factors (TGFα, TGFβ, IGF) which regulate the process of spermatogenesis. In the early stages of prenatal life these cells synthesize anti-müllerian hormone (AMH), which inhibits the development of müllerian ducts exerting influence on the determination of sex. Testosterone also has an effect on other organs important for reproduction – seminal vesicles and tissues associated with erection.

In fact, there are some discrepancies that comes from literature about the effects of obesity on sperm quality. Inconclusive results of trials are in a large extend due to the methodological reasons: the lack of projects aimed mainly on this issue, the impact of the accompanying diseases, material pre-selection (the studied subjects are often patients of infertility clinics), the imperfection of BMI and other factors. However, the deterioration of the quality of semen is certainly the most important and frequent cause of male infertility. A study performed in Europe including 2100 men from couples that sought help in fertility clinics presented oligozoospermia (sperm count < 15 million/ml) in 1018 of them (48.5%), and azoospermia (0 sperm cells per ml) in 340 (16%) of all subjects (16). Also observations carried out in couples undergoing assisted reproductive technology (ART) indicate that obesity in man leads to a reduction in the number of pregnancies and increases the incidence of lost pregnancies (17, 18). During the *in vitro* fertilization (IVF) procedure it was found that fertilization rate and the number of live born children were significantly lower in cases where the men were obese compared to slim fathers. There were no such differences when subjects participated in the intraplasmatic sperm injection (ICSI) procedure (19). It is believed that this observation may indicate an impairment of capacitation (preparation of the sperm for fertilization in the female genital tract) and sperm binding in case of men with excessive body weight. These observations confirm the previous data from animals studies (20). An important role in capacitation process plays tyrosine phosphatase (PTP1B), whose expression is regulated, inter alia, by cytokines produced in adipose tissue in obese subjects. Thus, also on this way excessive body weight negatively affects male fertility.

In chronic inflammation state associated with obesity the metabolic rate has to be accelerated to maintain normal biological processes in this condition. Unfortunately, this results in an increase in production of reactive oxygen species (ROS) and other active free radicals, which leads to damage to the structures of the DNA and cell membranes of germ cells. In animal studies, as well as in men participating in IVF procedures the relationship between increased BMI and intensity of oxidative stress, decrease in sperm motility, disturbances in acrosome reaction and complication of embryo implantation were demonstrated (20-22). Moreover, leptin that is in high concentrations reflecting high amount of fat mass directly, through its receptors, blocks spermatogenesis (23). Another, more prosaic mechanism in which obesity adversely affects sperm production is increase in local temperature under the influence of excess fat in the scrotum. Thisalso leads to abnormal course of spermatogenesis: reduced mobility and decreased sperm concentration, along with damage to their DNA, as well as to increased apoptosis of spermatogonia.

TRANS-GENERATIONAL INHERITANCE OF OBESITY – IMPACT ON MALE FERTILITY

Evidence based on animals studies reports that in I generation male descendants from obese fathers oxidative stress and its harmful effects in germ cells is found more often compared to offspring from fathers with normal BMI. In female descendants changes in mitochondria of oocytes and the increase in fat mass is observed. The inheritance mechanism of these phenomena explains the theory of "trans-generational epigenetic inheritance". This hypothesis says that the observed molecular changes are the result of obesity-dependent alterations arising during spermatogenesis, such as DNA methylation, histone acetylation, or changes in non-coding RNA. They are transmitted to the embryo and in consequence affect its further development (24, 25).

DNA methylation is a physiological process, necessary for the proper course of spermatogenesis, e.g. for inactivation of the X chromosome during meiosis. It is believed that in obesity, especially concomitant with its related diseases, e.g. in type 2 diabetes this process is disturbed. As it has been seen in animal studies hypomethylation of repeat elements and imprinted genes have been associated with increased levels of sperm DNA damage and decrease in the number of pregnancies (26). Histone acetylation is vital for spermatogenesis to proceed and is essential to relax chromatin structure that allows for the repair of the DNA. It was demonstrated that rodents maintained upon a high-fat diet exhibited abnormalities in histone acetylation and DNA damage in spermatids. Thus, epigenetic modifications associated with obesity can be transmitted and have an adverse effect on first and even second generation offspring development.

OBESITY – INSULIN RESISTANCE – DIABETES

There is a well-known close, direct relationship between obesity and type 2 diabetes. This association is

of causal connection: excessive fat mass, especially localized in the abdominal cavity (visceral obesity) triggers a several mechanisms leading to the development of insulin resistance, which, along with gradually progressive pancreatic β-cell function impairment are essential causes of diabetes. On the other hand, hyperinsulinemia leads to further increase in fat mass. Currently, diabetes affects approximately 9% of people all over the world. In the United States prevalence of this disease is 11.3% of adults – more than 1 person in 10. In Poland the number of diabetics is estimated to be approximately 9.5% of the whole population (27).

Already in the 10th century A. D. Persian doctor, philosopher and scientist Avicenna described "the collapse of sexual function in diabetes". Today the epidemiological studies and clinical observations confirm that these issues relates to 30-75% of all patients. For example in study performed in group of 857 men with diabetes aged 20-60 years married for at least one year, infertility have been found in 35.1% of the all subjects (primary infertility in 16%, and the secondary in 19% of them). These results appeared to be much worse when compared to the control group of healthy men ($p = 0.003$) (28). Adverse effects of diabetes on fertility is both direct and indirect. The disease disrupts the hormonal control of spermatogenesis and sperm production process itself. Moreover, it leads to vascular lesions and neuropathy with subsequent erectile dysfunction, ejaculation troubles and a decrease in libido. According to data form Massachusetts Male Aging Study (MMAS) ejaculation disorder in obese males occur 3 times more often when compared to the healthy subjects (29).

Factors affecting adversely male fertility associated with diabetes resemble those observed in obesity. In patients reduced number and damage to Leydig cells is found, which results in a decrease in the production of testosterone, a hormone of crucial importance for the proper course of spermatogenesis, libido and sexual behavior. Testosterone deficiency also results in lack of stimulation of Sertoli cells, which are necessary for the normal function of germ cells. In advanced diabetes abnormal course of spermatogenesis is observed, and visible symptom of this impairment is a reduction in the semen amount. Also diabetic neuropathy, resulting in a drop of the tension of smooth muscle of seminal vesicles, bladder and the ureters contributes to spermatogenesis disturbances (30). Serious structural defects of the sperm being the result of impairment in their maturation and apoptosis are observed. An important role in the pathophysiological mechanism of these changes plays oxidative stress induced by hyperglycaemia. Elevated blood sugar levels leads to increased mitochondrial oxidation and excessed release of peroxides and free oxygen radicals (ROS), on which germ cells containing in their membranes large amounts of polyunsaturated fatty acids are particularly vulnerable (31). It has been demonstrated the important role of endothelin and nuclear factor erythroid2-related factor (Nrf2) in the mechanism of intracellular release of ROS. As far as endothelin activates the NADPH oxidase in germ cells and stimulating the production of ROS, the Nrf2, being a transcription factor increases synthesis of intracellular scavengers of free radicals. Its beneficial, protective action becomes to be insufficient in diabetes (down regulation Nrf2 gene).

Another meaningful mechanism by which diabetes reduces the chance of getting pregnancy is germ cells apoptosis in men. As it has been shown in animal studies, hyperglycemia as well as free oxygen radicals are impulses triggering extrinsic signaling pathway and initiate apoptosis by transporting membrane receptor-mediated interactions. The receptors that belong the TNFα family contain so-called "death domain", responsible for the switching on the apoptotic signal. At the same time alternative apoptosis pathway – mitochondrial is activated. Mitochondrial membranes damage enables outflow of cytochrome c into the cytoplasm and formation of apoptosome with subsequent caspase system activation and apoptosis of the cell as a result of damage to its DNA, chromatin condensation and interruption of the cell membrane (32). The direct relationship between hyperglycemia and germ cell apoptosis in rodents with experimentally induced diabetes has been demonstrated (33).

Diabetes leads to destruction of germ cells also by the up-regulation of the autophagy. This process in normal conditions allows to maintain intracellular homeostasis by degrading and recycling of cellular organelles e.g. mitochondria or endoplasmatic reticulum. However, in diabetes under the influence of hyperglycemia-induced oxidative stress and excessive ROS production hyperactive autophagy could contribute to accelerated cell death (34).

CONCLUSIONS

Lifestyle changes, particularly unhealthy diet and decreased physical activity, often lasting from childhood, along with the progressive urbanization contribute to genuine obesity epidemic. Numerous studies show that in developed countries commonly occurring obesity is accompanied by almost parallel deterioration of male fertility. Adverse changes in the environment in today's world, which are derived from the marvel of industrialization impose on genetic predisposition as well as epigenetic changes, also often being the result of obesity of ancestors. A visible manifestation of the progressive nature of these issues is gradually deteriorating of sperm quality, requiring periodic verification of standards which it should meet in order to ensure successful procreation.

Understanding of a complex, multi-factorial etiology of a decline in male fertility, including realizing the role of obesity may be the first step on the road to effective prevention and combating the development of this socially significant problem.

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