Review Article

Diabetes Mellitus and Influences on Human Fertility

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Abstract

Background: Diabetes mellitus (DM) is a chronic, lifelong condition, while infertility is the disability to attain a pregnancy. They are directly connected to each other owing to the impact of this metabolic disease in humans' reproductive function.
Objective (Aim): This study aims to draw the attention of diabetes mellitus, both type 1 and type 2, in males and females in relationship to infertility.
Methodology: Extensive literature search in the electronic database "Pubmed", "Google Scholar", the website of "World Health Organization" (WHO) and Control Disease and Prevention (CDC) took place. There was no time restriction. A key criterion for the selection of articles was English and Greek language. Finally, forty one articles were included in the review and fifteen other were excluded because of their language or the irrelevant main idea.
Results: Diabetes mellitus cause increased damage in levels of nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) in males. As a result, the sperm DNA is affected, as well, leading to lower levels of fecundity and influencing reproductive health in general. Sexual dysfunction, libido dissociations, even vericocele are strongly associated with DM, as well. Diabetic women have problems of the fallopian tubes, ovaries, uterus and menstrual disorders. Lastly, respecting type 2 DM, it strongly affects renal physiology in men and it is mainly responsible for ovulation disorders and tubal obstruction in women.
Conclusions: Given the fact that diabetes mellitus strongly affects human' reproductive system, it is high time couples were informed about risk factors which contribute to the presence of infertility. Moreover, counseling support would be auxiliary, while the Assisted Reproduction is the alternative for infertile people, as well.

Key Words: diabetes mellitus, IDDM, NDDM, infertility, reproductive function.

Introduction

Diabetes mellitus is a disease which affects endocrine system and it is considered to be one of the most serious health problems to modern global health. Insulin-dependent diabetes mellitus's (IDDM) or type 1 diabetes' (T1DM) incidence in young people is almost twenty one per a hundred thousand person-years which were detected during a fifteen-year period while the first hospitalizations that took place for the US Navy's staff included ages from seventeen to thirty four. Nevertheless, IDDM's incidence in Japan may be from one to two per a hundred thousand. However, in some places of Finland it may be approximately fourty per a hundred thousand. As far as NIDDM's incidence is concerned, heterogeneity

relatively to the clinical signs and symptoms of the disease does not allow to accumulate enough data about it. Though, the prevalence of T1DM globally is estimated to be 5% to 7% (Lavender et al, 2010; Griffiths et al, 2008; Charron-Prochownik et al, 2006; Catalano, 2014; Radaelli et al, 2009).

According to the World Health Organization (WHO), in 2000 DM affected 177 millions of people all over the world. However, this number will have probably arrived at the three hundreds millions since 2025. This increase will be owed to ageing, obesity and population growth. Almost 90% of patients with noninsulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes mellitus (T2DM) are diagnosed before they reach the third decade of their life (Agbaje et al, 2007).

In children from Europe, incidence of T2DM rises almost by 3% per year and it is usually diagnosed during the first years of childhood (EURODIAB, 2000). As a result, a 50% raise in prevalence of NIDDM will take place in ten years from now (Silink, 2002). Thereafter, diabetes will afflict even more pre- reproductive or reproductive males. Consequences of DM may include effects on ejaculation and penile erection, lack of efficient endocrine control of spermatogenesis or even on spermatogenesis itself.

Furthermore, in the United States of America almost 15% of couples face serious difficulties in the attainment of a pregnancy and a male factor is responsible in half of them (Bhattacharya, Ghosh, Nandi, 2014; La Vignera, 2012).

Especially, infertility is the failure to get pregnant after trying one year at least or 6 months for women who are over 35 years old, without the use of any contraceptive measure and given the regular normal sexual intercourse. This is a complex health problem which is directly related to personal, financial and social problems. According to the World Health Organization (WHO) infertility as a medical condition concerns the 8-10% of couples worldwide (Saridi, Georgiades, 2010).

The incidence of infertility has increased considerably in recent decades all over the world. According to the literature, infertility is no longer just a result of health problems but choices of people's lifestyle nowadays, as well. As it is evidenced by recent studies, problems of the fallopian tubes, ovaries, uterus, and menstrual disorders are the main causes of infertility in women, while poor quality of sperm and varicocele are those which are responsible for infertility in men. Environmental, socio-economic factors, as well as advanced childbearing age and smoking increase the risk of infertility of a couple (Saridi, Georgiades, 2010). More specifically, regarding the association of diabetes with infertility, the fault lies in menstrual disorders caused by metabolic diseases such as diabetes mellitus. (Wu et al, 2007).

During recent decades, interest of health scientists has turned to investigating the factors that affect infertility of couples, firstly because more and more countries are facing demographic problems, secondly because the procreation and upbringing of children is an extremely important event in the life of every man. According to recent studies by the World Health Organization, human fertility has been declined significantly over the last 50 years. Although the incidence of infertility varies from country to country for various reasons, however, it is quite high. Particularly in Western European countries the incidence of infertility is amounted to 12% of couples who are in reproductive age (Benagiano, Bastianelli, Farris, 2006; Ziebe, Devroey, 2008; WHO, 2000; Boivin et al, 2007).

Methods

Extensive literature search in the electronic database "Pubmed" and "Google Scholar", the website of "World Health Organization" (WHO) and the website of the center for Control Disease and Prevention (CDC). Moreover, various scientific journals such as Journal Of Andrology, Midwifery Journal, Journal of Obstetrics and Gynecology and so on were used via search engine.

The main keywords which were used were the following: diabetes mellitus, IDDM, NDDM, infertility, reproductive function, male, female. There was a time restriction between 2000 and 2015. A key criterion for

the selection of articles was English and Greek language. Fifteen articles referred to other gynecological or endocrinological problems were excluded. Twenty more articles were excluded, as well, owing to the fact that they were based on dated references (from 1948 to 1999).

Results

Diabetes mellitus and its impact in infertility worldwide

Diabetes mellitus is correlated to metabolic disorders mainly as far as the regulation of carbohydrate metabolism is concerned. As a result, these abnormalities among other medical disturbances can cause problems in many vital organs such as eyes, nerves, kidneys and vessels, as well. People who have IDDM are thought to be genetically predisposed. This predisposition gets activated due to the environment, which induces an autoimmune response to beta cells of pancreas that produce insulin. Islet-cell antibodies are formed to destroy the population of B-cell in the pancreas, having therefore its impact in insulin secretion (Delfino et al 2007; Catalano, 2014).

DM is a disease that occurs more and more frequently around the world. Consequently, its presence in reproductive males is more often, as well. Subfertility constitutes an important health issue that concerns both the developed and the developing world. Particularly, approximately 16.7% of couples come up against with this problem and throw on doctors in order to receive the appropriate therapy that will lead them in pregnancy. Sperm disruptions may be the main cause or even just an instrumental factor for almost 50% of subfertile couples (Sharlip et al, 2002).

What is more, an obvious reduction in the quality of semen has been observed during the last 50 years. However, despite the fact that frequency of DM in subfertile men who attend clinical trials about fertility is largely unknown, according to past researches the prevalence of IDDM in them is estimated to be about 1%. Moreover, few investigations related to the impacts of DM on sperm fertility are bounded to semen analysis only (Agbaje et al, 2007).

How Diabetes Mellitus influence males' fertility

Diabetes mellitus influences males' reproductive functions. These disruptions can be delayed or even totally prevented through the appropriate and prompt therapy. The impairment respecting the T synthesis is owed to molecular basis, particularly at the level of Leydig cells. This impairment can affect other vital organs and tissues in human body. The interaction between Leydig cells which are associated with spermatogenesis and Sertoli cells which are related to the function of second sex glands, have an impact in specific anomalies in spermiograms of diabetic people. Parallel lesions related to DM may be caused or exacerbated by these disruptions through Central Nervous System (CNS) (hypothalamus-hypophysis) and endocrine profile. These disorders show dysfunction of homeostatic balance in the metabolism of carbohydrates (Delfino et al, 2007; La Vignera et al, 2009).

Sexual dysfunction in all its forms (reduced erection, impotence, and other libido dissociations) is an accompanying phenomenon of the diabetic disease. However, manifestations of these disorders are related to the regulation of carbohydrate metabolism and to the duration of disease. The duration of disease is not necessarily correlated with sexual dysfunction. Even carbohydrate metabolism remains within normal range in addition to other lesions, diabetes leads gradually but progressively to premature aging of body cells (Delfino et al, 2007; La Vignera et al, 2009).

Comparison of sperm from diabetic and nondiabetic men (through conventional and molecular techniques)

Researches in relationship with sperm quality in diabetic men have been narrowed to light microscopic estimation of semen parameters which are: semen volume, sperm count, motility and morphology. Elements from animals' clinical trials insist on the presence of DM's impact in male fertility (Loft et al, 2003). According to many researches, a remarkable mitigation of prolificacy is observed in many diabetic male animals (Agbaje et al, 2007; Ballester et al,

2004; Scarano et al, 2006), while sperm quality is getting deteriorated simultaneously (Amaral et al, 2006; Scarano et al, 2006). If the same results are applied to human male reproduction, a major problem in human fecundity that will be due to the increasing frequency of DM, will be posed, too. Notwithstanding diabetes mellitus' consequences in reproductive ability of young men, the necessary attention about it has not been received yet. From what it is already known worldwide, diabetic and nondiabetic men's fertility is never compared at a population. Nevertheless, there is data that testify the frequency of subfertility in men who has diabetes and the increase in reproductive results (for example in spontaneous abortion in their partners). Another approach to the light microscopic appraisal of sperm in order men's fecundity to be ransacked is the evaluation of sperm nuclear DNA (nDNA) or mitochondrial DNA (mtDNA) quality. These data are considered to be mediation markers of male fertility (Agarwal & Said, 2003; O'Brien J, Zini A, 2005). An appreciation of sperm nDNA fragmentation, mtDNA erasure number and size has been shown to have predictive value in assisted reproductive results (Lewis et al, 2004).

According to Padron's and Garcia-Diez's studies, DM intensely affects male reproductive performance. A decrease in all semen parameters (semen volume, sperm count, motility and morphology) has been observed in two studies of IDDM people (La Vignera et al, 2012). Nonetheless, Handelsman et al (1985) found that semen volume and aggregated sperm production are much lower in men with diabetes. Another study that took place among diabetic men discovered a rise in sperm concentration and overall sperm production but a consequent decrement in motility and no differences in sperm morphology. Vignon et al (1991) showed higher sperm gathering and not normal morphology with no differences to take place in motility. In the wake of the previous study, the researchers inferred that DM does not constitute a cause of infertility itself. This arises from the fact that diabetic men with normal semen parameters had obtained children, finally. In those studies that shows few negative effects of diabetes on semen, metabolic control and the upcoming neuropathy may exacerbate the situation that has already been created (La Vignera et al, 2009).

As it is supported by Trisini, the major differences between diabetic and nondiabetic males are molecular and not cellular. Given the restrictions of conventional semen analysis, sperm nDNA and mtDNA are considered to be molecular biomarkers of prolificacy possibilities. Additional independent data regarding sperm quality are provided by tests of genetic integrity (Trisini et al, 2004). In this way, abnormalities that are unclear in conventional semen profiles may be identified (Saleh et al, 2002). Nevertheless, these tests are not clinically popular because they are arduous, time consuming and expensive (Perreault et al, 2003). This study constitutes the first report of sperm nDNA and mtDNA quality in diabetic males. It recognizes significant elements about increased nDNA fragmentation and mtDNA deletions diabetic men's sperm. In conclusion, these results are worrying as they can influence fertility, risk of spontaneous abortion and health of the diabetic fathers' children (O'Brien, Zini, 2005; Evenson, Wixon, 2006).

Furthermore, lower levels of oxidative stress are required for mtDNA sperm damage than nDNA (Bennetts, Aitken, 2005) enhancing its importance as a sensitive index of sperm health (Lewis et al, 2004). In addition, oxidative stress constitutes one of the most significant factors in the pathogenesis of most of the chronic consequences of diabetes mellitus. In conclusion, the increased damage in sperm DNA results from diabetic males whose sperm that is getting developed is exposed to huge levels of glucose and as a consequence to oxidative insult (Nishikawa, Edelstein, Brownlee, 2000; Piconi, Quagliaro, Ceriello, 2003; Wiernsperger, 2003).

How Diabetes Mellitus influence females' fertility

Diabetes mellitus can affect female fertility, as well. Even if there are no enough objective elements, the establishment of insulin therapy contributed to the reduction

of amenorrhoea in women who has diabetes, therefore, improving female fertility. Amenorrhea was a usual phenomenon for women with uncontrolled diabetes and it was responsible for the increase of infertility, until the introduction of insulin therapy took place in 1923 so that it reverse this situation

Endocrine problems which lead to faulty ovulation, tubal disease that intervenes with oocyte pickup, unexplained subfertility in fertilization areas and impairment in gamete transport and implantation, play a significant role in the cause of infertility (Lavender et al, 2010; Griffiths et al, 2008; Charron-Prochownik et al, 2006).

Endocrine Abnormalities and Defects of Ovulation

Women that developed diabetes mellitus during prepubertal age, have delayed menarche and this means that a disturbance of the hypothalamic – pituitary – gonadal axis may occur. Moreover, it has been proposed that menopause happens prematurely in diabetic females. Approximately 30% of insulin – treated women with diabetic mellitus face menstrual disturbances, and the appearance of diabetes seems to be a significant subduction factor. Abnormalities of the hypothalamic – pituitary – gonadal axis are mentioned respecting reproductive diabetic females and these are the reduction of basal prolactin secretion and the impaired prolactin response to metoclopramide. In conclusion, these disorders were possibly owing to the elevated dopaminergic inhibitory activity on lactotrophs (Radaelli et al, 2009).

In well – controlled diabetic females their menstrual period is regular, has basic gonadotropin levels and the gonadotropin response to the gonadotropin – releasing hormone (GnRH) is considered to be normal. However, the levels of serum glucose have been correlated with the luteinizing hormone's (LH) reply to GnRH, pointing out the probability that pituitary operation is affected by current glucose levels. Furthermore, according to data that comes from clinical studies in diabetic animals, hypothalamic pituitary may be influenced by the released steroids. This effect may be partly reversed by insulin therapy (Radaelli et al, 2003).

Moreover, disturbances of sex steroid secretion are also directly related to IDDM. Djursing et al (1985) found increased levels of androstenedione and testosterone while the appearance of serum oestradiol was normal. Menstruating females who have regular period have also increased levels of androgen. On the side, it was concluded that the origin of androgen was the ovaries. Owing to the fact that these alterations were dependent upon changes in sex, hormone and binding globulin, hirsutism or menstrual disorders did not happen at all (Charron-Prochownik et al, 2006).

Pursuant to Djursing (1987) the main reason that leads diabetic females to amenorrhoea is the elevated dopaminergic inhibition of gonadotropin excretion. In spite of low levels of follicle – stimulating hormone (FSH) and basic oestradiol, there reaction of FSH to GnRH is normal. Additionally, there are disorders respecting to LH pulsatility and its response to GnRH is smoothed. Nonetheless, the exclusion of dopamine may enhance the FSH levels (Ballester et al, 2004).

Type 2 Diabetes mellitus and infertility

The pathogenesis of NIDDM is not very clear, but it is speculated that insulin resistance preexist of the disease. Moreover, positive family history plays the most important role in the appearance of diabetes. Investigators are not yet sure whether insulin resistance is the only reason for the development of NIDDM or if it just reveals a main deficiency of B-cell. The most important issue respecting to diabetic males' reproductive function regards the cause, incidence, diagnosis and treatment of disability. Furthermore, male reproductive system is combined with renal physiology and it is composed of pretesticular, testicular and post- testicular nephridia.

In particular, pretesticular nephridia are necessary for hypothalamic-pituitary-gonadal axis and endocrine control, testicular nephridia are responsible for spermatogenesis and post- testicular nephridia are combined to ejaculation.

Diabetes mellitus may be disastrous for all or any of these aspects (Bener et al, 2009).

Relationship between delayed conception and type 2 diabetes risk

There are reasonable underlying mechanisms which combine inflammation and insulin resistance. According to a research conducted by Tobias in 2015, 5,3% of participants developed noninsulin dependent diabetes mellitus during the last 24 years (1989-2013) of follow-up. After age, family's history of diabetes, BMI, oral contraceptive use, marital status and lifestyle factors have been estimated it arose that women who came up against infertility was correlated with a 20% higher risk of developing DM, compared with fertile women. The main causes of these females' infertility associated with higher risk of diabetes were the ovulation disturbances and the tubal factor. On the side, even if the subfertility in men was related to a moderately higher diabetes risk, cervical factor and endometriosis were not connected with each other. In conclusion, subfertility which is due to ovulation disorders and tubal obstruction, is strongly related to a higher risk of NIDDM (Tobias et al, 2015).

Is male fertility associated with type 2 diabetes mellitus?

According to a study that was completed by Bener in 2009, the predominance of type 2 diabetes mellitus in men from Qatar is strongly associated to infertility in these males. What is more, the increase observed in frequency of subfertility indicates a serious public health problem (Bener et al, 2009).

As far as the research's results are concerned, the predomination of infertility in Qatari men who suffered from type 2 diabetes mellitus was about 35%. Diabetic men appeared higher percentages of primary and secondary subfertility than non-diabetic men, which were 16% and 19% respectively. In addition, Qatari diabetic males who took part in the study manifested higher secondary subfertility than primary subfertility. Moreover, almost half of the diabetic infertile males were overweight and the 30% of them were obese. Also, it is showed that diabetic subfertile males (46%) smoke more ordinarily than diabetic fertile males (34%). Last but not least, according to multivariate analysis it is proved that age, smoking habits and obesity were the major contributors for infertility in diabetic men. To conclude, obesity was the main reason which resulted in subfertility (Bener et al, 2009).

Discussion

Many reports in the bibliography regards to diabetes mellitus' consequences in relationship with the endocrine control of spermatogenesis. However, these studies are under contradiction and concerning the abnormalities reported, they definitely do not constitute the main reason for which damage in reproductive function happens. Nevertheless, the fact that diabetes contributes to male's sexual dysfunction and consequently, to subfertility is undeniable (Baccetti et al, 2002; Ballester et al, 2004).

Particularly, according to Greenberg and associates' research as far as the causes of infertility are concerned, it showed that among 425 men who were assessed for subfertility, only the 3 (0.7%) of them had T1DM. More specifically, the two of them mentioned retrograde ejaculation and the other one mentioned sexual dysfunction. Low incidence of insulin–dependent diabetes mellitus was noticed, as well, with the percentage of subfertile men who were diabetic too, to amounts to 1,1% (five diabetic men among 466 subfertile men). This result regards people who were up to twenty six to forty four years old. The three of these diabetic patients had retrograde ejaculation, the one had failure of emission and the other one mentioned oligoasthenospermia and varicose in veins, as well, but without the subfertility's cause of the last one to be clearly identified, as it could be both the diabetes and the vascular lesion. From the above it is indicated that diabetes plays a minor role in male fertility. Last but not least, the incidence of IDDM among men whose age was from seventeen to thirty four is 0.02% whereas the incidence of male infertility among them was about 7.5% (La Vignera et al, 2012).

According to Kjaer's research (1992), the total amount of pregnancies and sterility's

incidences was approximately the same (17%) in both diabetic and nondiabetic women. More specifically, insulin-dependent diabetic women had fewer pregnancies (1.4 vs 1.7) and fewer births per pregnancy than nondiabetic control subjects. In addition, more diabetic women were nulliparous (48% vs 38%). Regarding to diabetic pregnancies, half of them were planned and diabetic women mentioned that diabetes had an impact on their decision and try to have a child (Griffiths et al, 2008).

In respect to Delfino's study whose object was the prevalence of diabetes mellitus in males of couples who faced subfertility, seminal and biochemical parameters of 512 men aged 25 to 52 years old are estimated so that the appropriate therapy will be determined in order the pregnancy to be achieved. As a result of this study, the DM's prevalence in the subjects was 1.18%. Particularly, there were four men with NIDDM and two men with IDDM. The three of the four non- insulin dependent diabetic males and the one of the two insulin dependent diabetic males mentioned normal ejaculation. There was detected alteration of semen's quality, whereas the most remarkable results were in relationship to progressive motility. However, despite the fact that the morphology of sperm was reduced, too, the concentration of it did not present substantial changes. As therapy could be used a similar one to this which is used for other dyspermic males of subfertile couples. On the side, the other two subjects had to come up against retrograde ejaculation and they took part in vitro fertilization programs or in intrauterine insemination. Lastly, diabetic males presented higher levels of fructose in regard to the biochemical seminal profile respecting the nondiabetic subjects. Last but not least, the low prevalence of DM among this group of people is owed to this specific range of age. In conclusion, DM affects the quality of sperm and the ejaculation mechanism, as well (Delfino et al, 2007).

In addition, another semen analysis reported to twenty seven diabetic subjects in the mean age of thirty four to thirty six and twenty nine nondiabetic subjects in the mean age of thirty three to thirty four, was conducted. In accordance with the results of the study, there was a small but major decrease in semen volume in diabetic males, while there were no other differences comparing the semen parameters between the two groups. Moreover, it was performed an important increase in diabetic subjects' mean nDNA fragmentation and mtDNA damage which can influence the reproductive function of these males, in contrast to nondiabetic subjects (Agbaje et al, 2007).

Conclusions

Diabetes Mellitus is related to increased sperm nDNA and mtDNA damage which can affect the reproductive ability of men who suffer from this (Agbaje et al, 2007). Furthermore, it influences the quality of sperm and the mechanism of ejaculation (Delfino, 2007). What is more, regarding insulin-dependent diabetic women, they may conceive normally but they have fewer pregnancies and births per pregnancy than control subjects. For this reason, informing couples about the risk factors that contribute to the existence of infertility is the cornerstone for the prevention of it (Saridi, Georgiadi, 2010).

Despite worries about incapacity of attaining a pregnancy, the effects of diabetes mellitus on males' reproductive function have been intensely ignored, so far. Apart from the semen volume no other differences, as far as the semen is concerned, exist between diabetic men and control subjects. However, there is elevated damage in diabetic men's levels of nDNA and mtDNA. The fact that sperm DNA impairment affects men's fertility and reproductive health should be taken into consideration. Last but not least, further studies regarding to the accurate nature of this damage, the causes behind it and the evaluation of its clinical importance are vital and necessary to take place (Agbaje et al, 2007).

Couples that face subfertility problems should receive counseling support. It is a vital intervention for these people's mental health owing to the fact that it gives them the ability to express problems that according to them, are attributed to their inability to have children. In this way, they share their fears and anxiety about this situation and they do

not hesitate to make questions so that they resolve all their queries in regard to their marital and sexual relationship, as well (Lee et al, 2000).

In modern times, medical science and particularly the Assisted Reproduction contributes significantly to the fight against infertility. Assisted reproduction occurs when methods and techniques are used for achievement of fertilization without, though, sexual intercourse to takes place (Benagiano, Bastianelli, Farris, 2006; Ziebe, Devroey, 2008; WHO, 2000; Boivin et al, 2007).

However, in Greece, the insurance arrangements for the investigation and treatment of infertility are insufficient and the informing of the population concerning this medical issue is incomplete. As a result, the attempt to reduce the country's infertility incidents becomes really difficult to get completed (Lee et al, 2000).

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