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Perilous influence of diabetes mellitus on fertility: possible and progressive future approaches and treatments to cure

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A B S T R A C T

Nowadays a huge number of people suffer from infertility throughout the world due to diabetes and irregular life-style. The number reaches 60-80 million globally. Diabetes mellitus is a chronic non-curable but manageable disease. According to the International Diabetes Federation (IDF) report released in November 2021, the number of adult people suffering from diabetes mellitus (DM) has risen from 108 million in 1980 to 537 million in 2021 and according to the previous IDF report, it was about 387 million in 2014 and 463 million in 2019. Type1 diabetes causes decrease in insulin level and degrades essential proteins of the body. Type 2 Diabetes Mellitus is the most common form of the diabetes mellitus and it was formerly known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. This T2DM comprises a cluster of dysfunctions that is generally characterized by hyperglycemia and it results from the combined effect of relative insulin insufficiency or insufficient secretion of insulin, insulin resistance and excessive or uncontrolled glucagon secretion. The study focuses on diabetes associated infertility and treatments. Throughout various physiological mechanisms type1 and type2 diabetes mellitus affect male and female infertility. This finding thus creates a relationship between diabetes mellitus and infertility and possible effective treatments.

Keywords: Type 1 Diabetes · Type 2 Diabetes · Hyperglycemia · Infertility · Treatment

1. Introduction

Diabetes mellitus is a metabolism-related disorder consisting of multiple etiology which is distinguished by chronic hyperglycemia along with the disturbances of carbohydrate, protein and fat metabolism which results defect in the action of insulin secretion and insulin function or both that is diabetes is a chronic non-communicable metabolic disorder that happens either when the pancreas does not produce sufficient insulin or when the body cannot successfully utilize the insulin it produces. It is caused by genetic, environmental, and other factors [1-3]. Thus, diabetes is named as 'silent killer' causing long-term damage and failure of most of the organs. Symptoms include weight loss, thirst, blurring of vision and polyuria *etc*. In absence of effective treatment diabetes can cause death of affected individual. Often severe symptoms are not seen but it can be lethal if left untreated. The prolonged effect of diabetes leave impact on eyes, kidneys and heart causing retinopathy, nephropathy, cardiopathy respectively. Diabetes can also cause serious problems related to infertility. Measuring the severeness 14th November is celebrated as 'World Diabetes Day' to promote awareness. IDF estimated that the number will increase up to 783.2 million in 2045. Now 53.7 crore people aged between 20-79 are affected by diabetes. The number of affected individuals will increase to 64.3 crore in 2030 to 78.3 crore in 2045. Till date, sixty-seven lakh people died after being affected by diabetes. One child per six children becomes affected in diabetes during gestation [4-7].

2. Overview of diabetes associated infertility and treatments

Fertility is the term involved with the capability to give birth or by settling a clinical pregnancy. Worldwide around 186 million people are now suffering from infertility. A man or woman can be treated as infertile when they are unable to conceive a child normally. Numerous factors are responsible for infertility. Infertility can be cured by medication, surgery or hormonal therapy based on the factors influencing it. Infertility can be classified into two types- primary infertility and secondary infertility. Primary infertility occurs when a female accomplishes all the criteria of infertility as she never possesses a clinical pregnancy. Secondary infertility occurs when a female is unable to conceive a child but she is previously diagnosed with at least one clinical pregnancy. Besides, males also show these two types of infertility. Secondary infertility is most prevalent among women. Males are responsible for 20-30% of infertility cases. Worldwide, it is estimated that 8-12% reproductive-aged people are suffering from infertility [8,9].

3. Research methods

This current review is based on a number of research papers and study reports to accomplish an association between the adverse effects of diabetes on fertility which supports the search for ways to reduce these harmful side effects. If the diabetes associated infertility can be identified properly, there is a better chance of being able to treat the problem. This review targets to achieve a link between how diabetes mellitus impose effects on male and female fertility. Diabetes mellitus may affect male and female reproductive function at multiple levels. Data provided in this review were obtained from primary sources with main emphasis on diabetes and infertility. The review has been separated into multiple subheadings for the consideration of several significant issues.

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4. Results and Discussion

4.1. Influence of diabetes mellitus on fertility

Diabetes can be of two types *viz*., Type1 or insulin dependent diabetes and type2 or insulin-independent diabetes. Type1 diabetes is caused by T-cell-mediated autoimmune destruction of pancreatic β cell which produce the blood sugar controlling enzyme insulin. Heredity, age, race also play crucial roles for causing diabetes. Type1 diabetes causes decrease in insulin level and degrades essential proteins of the body. This disease is most frequent in children and young adults at a rate of 3% per year. About 70000 children are affected by type1 diabetes mellitus worldwide. Islet-targeting autoantibodies that target some proteins which are associated with secretory granules of BETA (β) cells act as biomarkers of T1DM-associated autoimmunity by which the risk of developing T1DM in any individual can be identified and studied further. These proteins are glutamic acid decarboxylase, insulinoma-associated protein 2 (IA-2), insulin and zinc transporter 8. The remedy is not available, so patients depend on lifelong insulin injections; novel approaches to insulin treatment, such as insulin pumps, continuous glucose level checking are in advancement. A few clinical trials for anticipating type 1 diabetes are also right now in advance or being planned [10]. Type 2 Diabetes Mellitus is the most common form of the Diabetes Mellitus and it was formerly known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. This T2DM comprises a cluster of dysfunctions that is generally characterized by hyperglycemia and it results from the combined effect of relative insulin insufficiency or insufficient secretion of insulin, insulin resistance and excessive or uncontrolled glucagon secretion [11]. Type 2 DM is responsible for 90% to 95% of all diabetes diagnoses. Type 2 DM is basically due to lifestyle and behavioural factors and genetics [12]. Older age, obesity, sedentary lifestyle, physical inactivity, stress, cigarette smoking and alcohol consumption are all risk factors for T2DM [13]. Obesity is an important factor which contributes to roughly 55% of cases of T2DM [14].

4.2. Possible treatments of diabetes

There are various treatments options from synthetic medicines to natural compounds to manage diabetes. Various medications are also there to treat infertility. The possible remedies are summarized below.

4.2.1. Treatment of Type 1 Diabetes

Diabetes cannot be cured, it can be managed somehow. The main target is to keep the blood sugar level as normal as possible that is between 80-130 mg/dl before taking meals and around 180mg/dl after taking meal. One who suffers from type1 diabetes mellitus should follow an insulin therapy. Insulin cannot be taken orally to reduce blood glucose level as there are numerous stomach enzymes to breakdown the insulin by deactivating their normal working process. Therefore, insulin is taken via injection or insulin pump. Insulin pen or syringes and needles are used to enter the insulin inside. An insulin pump is a programmable device to inject specific amount of insulin from a reservoir through a catheter inserted under the abdomen. There are different types of insulin available which include:

- SHORT-ACTING INSULIN: Short acting insulin is a regular type of insulin which starts its activity 30 minutes after being injected and lasts for about four to six hours. Examples- HumulinR.
- RAPID-ACTING INSULIN: This type of insulin starts expressing its activity 15 minutes after being injected. It also lasts for four hours as its peak activity reaches sixty minutes after the time of injection. Examples- Glulisine, Aspart.
- LONG AND ULTRA-LONG-ACTING INSULIN: This type of insulin gives prolonged coverage for about 14 to 40 hours. Example- Glargine.
- INTERMEDIATE-ACTING INSULIN: This insulin starts expression of it within 1 to 3 hours after injection and lasts for 12 to 24 hours. Examples- HumulinN.

One has to check his/her blood sugar level at least four times in a day before taking meal, after taking meal, before going to bed, before exercise as recommended by the American Diabetes Association. Continuous glucose monitoring can be done by attaching a needle beneath the skin to check blood glucose and to prevent low blood glucose level.

People those have diabetes along with high blood pressure ranges between 140-90mmhg angiotensin converting enzyme inhibitors to keep kidney in proper function. Taking aspirin regularly leave good effect on people having type1 diabetes as they have increased risk of heart attack. Various cholesterol-lowering drugs can also be taken. A healthy lifestyle and healthy eating can help to manage diabetes. A diet full of nutritious fruits, vegetables and whole grains is very much needed. Regular walking and 150 minutes of aerobic exercise within a week is very much useful for patients with type1 diabetes. A successful pancreas transplant is done sometimes for those patients who are unable to manage diabetes. There is no longer need to inject insulin but this procedure to manage diabetes can be dangerous sometime. Islet cell transplant helps new islet cells to form and helps to produce insulin naturally. A donor is needed in this process [15].

4.2.2. Treatment of Type 2 Diabetes

Type2 diabetes can also be managed by following a strict diet, regular exercise, maintaining a healthy lifestyle and taking suitable medications. Various drugs are available in the market to manage diabetes. Most popular among them is metformin and thiazolidenidiones. Metformin is under the biguanide group and it became the first orally active medicine for treatment of type2 diabetes. Metformin imparts minimum side-effects and possess minimum risk of hypoglycemia. Metformin is well tolerated

among individuals of different ages. Metformin acts via stimulating adenosine mono phosphate (AMP) activated protein kinases which are involved in absorption of glucose and prevent gluconeogenesis by modifying different mitochondrial enzymes. Metformin also induces weight reduction in obese diabetic people [16]. Thiazolidenidiones is an insulin sensitizer by making body tissues more sensitive to insulin [17]. While sulfonylureas induce pancreatic insulin production and they have role in gluconeogenesis also [18]. They also inhibit lipid breakdown of the body. But these conventional medications cause many side-effects. So, these synthetic medicines are replaced by similarly active phytomedicines which have less side-effect. Over 800 herbs and 450 plants are identified as anti-diabetic agents to treat diabetes. When chemical treatment fails to cure diabetes these phytomedicines are used as they are widely accessible. These phytomedicines are environment-friendly also. some of these phytomedicines include marmelosin from *Aegle mermelos*, naringenin from *Ajuga iva*, allicin from *Alium sativum*, azadirachtin from *Azadirachta indica etc* [19].

4.2.3. Treatment of Diabetes associated infertility

Antioxidant therapy which prevents generation of Reactive Oxygen Species (ROS) is used to treat diabetes associated infertility [20]. Diabetic men who have infertility also seek for assisted reproductive technology like in vitro fertilization. Around 51.2% infertility is cured by using assisted reproductive technology [21,22]. If the cause of diabetes associated infertility can be identified, there is a better chance of being able to treat the problem.

5. Conclusions and recommendations

Diabetes mellitus have been known for its degradative effect on infertility. Those patients who are unable to manage diabetes along with fertility problems should receive counselling support. One who suffers from type1 diabetes mellitus should follow an insulin therapy. Type2 diabetes can also be managed by following a strict diet, regular exercise, maintaining a healthy lifestyle and taking suitable medications. Metformin is under the biguanide group and it became the first orally active medicine for treatment of type2 diabetes. So, doctors and endocrinologists should aware their patients about this fertility issues by proper counselling. Safe and effective medication should be taken who are suffering from infertility issues. They should seek for assisted reproductive technology and in vitro fertilization. However, it is very difficult to reduce infertility associated with diabetes of country's every man and woman. As diabetes is regarded to cause infertility so if diabetes can be managed somehow infertility will be less. So, when individuals are diagnosed with infertility due to diabetes, they should immediately seek treatment.

Conflict of interest

The author declares that there is no conflict of interest in this manuscript.

Data availability

The author confirms that all data collected or analyzed during this study are included in this published article.

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