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Impact of Diabetes on Male Fertility: The Role of Medications and Medicinal Plants

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ABSTRACT

Diabetes mellitus is a common metabolic disease that significantly reduces male fertility through several pathways, including testicular dysfunction, oxidative stress, endocrine dysregulation, and chronic inflammation. Although pharmaceutical measures are necessary to keep blood sugar levels under control, some antidiabetic medications may unintentionally affect the health of men's reproductive systems. On the other hand, lifestyle changes, such as dietary changes, regular exercise, and good stress management, are non-invasive methods that improve fertility and reduce diabetes-related reproductive dysfunction. Furthermore, medicinal plants' antioxidative, anti-inflammatory, and endocrine-modulating qualities and their bioactive phytochemicals have made them prospective therapeutic agents that promote spermatogenesis and lessen testicular damage. To address diabetes-related infertility, this study methodically examines the interactions between antidiabetic medications, lifestyle changes, and phytochemical therapy, highlighting the possibility of the integration of various strategies. Additionally, it promotes thorough study to improve treatment approaches and maximize the reproductive results for diabetic males. Diabetes can affect epigenetic modifications during sperm spermatogenesis, with these dysregulations potentially being inherited through the male germline and passed across multiple generations. This inheritance may elevate the risk of diabetes in offspring.

1. Introduction

Chronic metabolic disease Diabetes mellitus is a rapidly expanding worldwide issue that has significant social, health, and financial ramifications. Obesity and population aging are the primary causes of the rise[1] .Type 1 and type 2 diabetes mellitus are the two most common subtypes of the disease, and the therapy of each is based on etiopathology. People with concurrent pharmacological therapy, such as corticosteroids, or a coexisting genetic predisposition are more likely to experience hyperglycemia[2]. The burden of non-communicable diseases (NCDs) is steadily rising, making them serious health issues. One

of the primary categories of chronic non-communicable diseases is diabetes mellitus. NCDs were responsible for 43% of the global illness burden and 60% of mortality in 2000. According to predictions, by 2020, the burden of NCDs will account for around three-quarters of all deaths and 60% of all diseases worldwide. According to the International Diabetes Federation (IDF), cardiovascular complications account for between 75 and 80 percent of the deaths of diabetics [3] .Diabetes mellitus is a significant risk factor for the early onset of coronary heart disease and a leading cause of morbidity and mortality. Diabetic complications include peripheral neuropathy, retinopathy, and nephropathy. [4]. It has long been known that male fertility can be harmed by hyperglycemia. In the eleventh century, doctors had previously observed that men with dysregulated glucose metabolism had issues with their sexual functions and had trouble fathering children; they called this condition a "collapse of the sexual functions" of the male. Although diabetes affects glucose metabolism, a crucial component in spermatogenesis, the exact mechanisms by which DM results in male infertility remain unclear [5]. Fig.1. Since sperm cells are immotile in the testis, they require energy to acquire and retain motion competence following epididymal maturation. Sperm use a large amount of adenosine triphosphate (ATP) to keep moving. Sperm mostly use carbohydrates as fuel, except a few metabolites including lactate and citrate as an energy source that contains fructose, glucose, and mannose. Anaerobic glycolysis and oxidative phosphorylation are the two primary metabolic processes that contribute to energy production. Both type 1 and type 2 diabetes in men impact spermatogenesis and testicular function. [6] To sustain both basic cellular activity and specialized processes like motility and fertilization, sperm rely on glucose as fuel. In order to sustain spermatogenesis, serotonin cells must also break down glucose to make lactic acid, and this process is essentially regulated by hormones including insulin, testosterone, and FSH. Several membrane proteins, including active transport (sodium-dependent glucose transporter [SGLT]) and passive transport (glucose transporter [GLUT]), facilitate the movement of glucose between the blood and tissues [7].

2. Biguanides, sulfonylureas, meglitinides, thiazolidinediones/glitazones, bile acid sequestrants, amylin mimetics, sodium-glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP1), α-glucosidase inhibitors, and dipeptidyl peptidase 4 (DPP4) inhibitors are among the chemical drugs used in a variety of study designs, experimental models, and compounds[8]. Male infertility may result from diabetes mellitus through pre-, testicular, and post-testicular mechanisms. The first involves DM patients developing hypogonadism through peripheral (changes in Leydig cell activity) and central (hyperleptinemia or changes in hypothalamic GnRH pulsatile release in overweight or obese patients) processes, which lower serum levels of testosterone and gonadotropin[9]. Diabetes-related insulin resistance and insufficiency can harm the pituitary, hypothalamus, gonads, and perigonads. In addition to causing testicular atrophy, stromal cell atrophy, seminiferous tubule damage, spermatogenic cell damage, and

other structural injuries of the male reproductive organs, this can decrease the secretion of sex hormones such as gonadotropin-releasing hormone, follicle-stimulating hormone, luteinizing hormone, and testosterone. These behaviors may impact male fertility and reproductive health. [10] Table 1.

3. **TREATMENT**: The inability to have a child is a personal tragedy for couples suffering from infertility. These couples use both traditional medicine and modern therapies as treatment. In developing countries, traditional medicine particularly medicinal plants thanks to their accessibility, availability, and affordability are generally the first recourse of infertile couples. Several plants are empirically used to treat different aspects of male infertility such as sexual asthenia, libido (sexual desire), erectile and ejaculatory disorders, and sperm abnormalities (azoospermia, oligospermia). The biological activities of many of these plants were confirmed by in vitro, and/or in vivo animal studies and in humans[24].The aqueous extract of ***Astragalus membranaceus*** and ***Acanthopanacis senticosi*** at 10 mg/ml increased the motility and viability of infertile male sperm in vitro. Decoctions of *Semen cuscutae*, *Rhizoma curculiginis* and *Radix morindae* officinalis improved sperm motility and the stabilization of sperm membranes in vitro, indicating that herbal decoctions may Androl. 19:148-158 151 be beneficial in promoting sperm function for intra-uterine insemination (IUI) and in vitro fertilization (IVF)[24] The treatment of male infertility has used and still uses phytomedicines for several reasons: improvement of natural fertility through the effect of phytomedicines on different compartments of the male reproductive system, use of phytomedicines to improve sperm parameters for new reproductive technologies (NRT). Physicians treating male infertility need to know about the medicinal plants whose relevant scientific investigations have been done and how to combine this therapy with the modern one[24]. Compared to earlier research, the herb combination has fewer adverse effects and is easier to manage. Because of its herbal structure, low problems, and inexpensive cost of therapy, it is linked to great satisfaction. The herbal mixture appears to influence the treatment of male infertility and improve sperm parameters. Therefore, it is advised to try compound herbal medicine as a suitable and safe option before using art[25]. Because they directly affect both natural and aided conception, the assessment of semen parameters and the integrity of spermatozoa's deoxyribonucleic acid (DNA) are frequently researched from a clinical standpoint. However, recent research focusing on molecular pathways other than glucose transport in testicular cells offers fresh perspectives on how diabetes mellitus affects male reproductive health. The glucose-sensing apparatus in testicular cells responds to changes in hormone levels and has multiple defenses against hyperglycemic and hypoglycemic episodes. Furthermore, proper spermatogenesis depends on the metabolic cooperation of testicular cells. The primary constituents of the blood-testis

barrier, Sertoli cells (SCs), are in charge of both the physical support of germ cells and the synthesis of lactate, which the growing germ cells subsequently metabolize[26]. Reducing infertility and enabling the afflicted to enjoy their sexual activities regardless of the boundaries set by the diseased are the goals of treating diminished sexual response, ED, and retrograde ejaculation. In addition to medicine, physical, psychological, and surgical treatment may be the main emphasis of the treatment. By altering any reversible physical activity that is causing sexual dysfunction, physical treatment improves the subject's overall health. The goal of psychological treatment is to address the fundamental and secondary psychological responses that are causing the issue. Penile prosthesis implantation and penile vascular regeneration are examples of surgical treatment for erectile dysfunction. Rebuilding the bladder vesical sphincter is one surgical method for correcting retrograde ejaculation. Drugs frequently used to treat ED are referred to as medication. These include Vardenafil (Levitra, Staxyn), Tadalafil (Cialis), Sildenafil (Viagra), and Avanafil (Stendra)[27].

4. **ANTIOXIDANT THERAPY** Male factors account for almost half of occurrences of infertility. One of the primary reasons of male infertility is oxidative stress, which is defined as an imbalance in reactive oxygen species (ROS) and antioxidant levels. The physiological processes of sperm, such as capacitation, hyperactivation, and acrosomal response, require a trace quantity of ROS. High ROS levels, however, can result in infertility by oxidizing sperm proteins and inactivating enzymes in addition to causing lipid peroxidation or DNA damage. Lifestyle factors are the primary source of oxidative stress (OS). Other major sources of ROS include genetic mutations, inflammatory causes, immature spermatozoa, and changes in sex hormone levels. Given that OS results from a deficiency of antioxidants and its adverse effects in semen, lifestyle modifications, and antioxidant supplements can be beneficial treatment strategies to address this issue. Using a variety of processes, including lipid peroxidation, DNA damage, disorders of the male hormone profile, inflammation, and varicocele, the current study sought to characterize physiological ROS generation, the effects of genetic and epigenetic variables on the OS, and male infertility. Lastly, the functions of botanicals and oral antioxidants in managing OS in male infertility were discussed[28].
5. **HORMONAL THERAPY** The high prevalence of hypogonadotropic hypogonadism, which has recently been defined as functional hypogonadism and is characterized by low testosterone associated with inappropriately normal gonadotropin levels, is one of the effects of type 2 diabetes mellitus (T2DM)-induced insulin resistance and chronic hyperglycemia on the hypothalamic-pituitary-gonadal axis in men. Several factors, including insulin resistance, glycemic management, and concurrent sleep apnea, may contribute to the pathogenesis of this hormone imbalance. Still, the degree of central or visceral obesity and the resulting inflammatory state plays a major role. Several medications, including sodium-glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide-1

receptor agonists, have been created to treat type 2 diabetes. All seem to work well to improve blood glucose regulation by reducing inflammation and swelling. Most appear to lower the chance of microvascular and macrovascular damage brought on by uncontrolled diabetes[39].

6. **LIFESTYLE MODIFICATION** Finding effective management and prevention measures is unavoidable given the deteriorating trend of male fertility parameters from a worldwide perspective and the uncertainty surrounding its diagnosis. Numerous medical diseases are being caused by improper lifestyle choices, which are gradually causing human systems to deviate from normal equilibrium. Due to its complex structure, superficial anatomical location, high sensitivity to different physical conditions (such as pressure and temperature), and immunological privilege, the male reproductive system is susceptible to negative effects from environmental factors and unhealthy lifestyle choices. Male reproductive tissues are negatively impacted directly by several bad habits and morbid lifestyle factors, or they are indirectly disrupted by endocrine regulatory axes[30].
7. **PHYSICAL ACTIVITY** One of the most relevant consequences of diabetes mellitus is temporal or complete infertility which can happen in young individuals. Therefore, the current systematic review aimed to investigate the effects of exercise to reduce the impact of Type 2 Diabetes Mellitus (T2DM) in seminal quality and related parameters. Physical exercise increased sperm count, motility, and morphology, as well as improved testosterone, Luteinizing Hormone (LH), and Follicle Stimulating Hormone (FSH) levels. Moreover, physical exercise intervention reduced the percentages of sperms with negative Tubular Differentiation Index (TDI) and Spermiogenesis Index (SPI), DNA fragmentation, and also ameliorated the diabetes-induced apoptosis and improved sperm apoptosis index[31].
8. **WEIGHT MANAGEMENT** A higher prevalence of obesity in the male partner is linked to male factor infertility. Men who are obese have higher levels of estrogen and lower levels of androgen and SHBG. The degree of obesity is correlated with lower inhibin B levels, which do not coincide with corresponding rises in FSH. This intricately changed reproductive hormone profile raises the possibility that endocrine dysregulation in obese men could account for the higher risk of infertility and altered semen characteristics. Changes in lifestyle variables, increased risks for sexual dysfunction, and altered retention and metabolism of environmental contaminants are further characteristics of male obesity that may raise the chance of infertility[32].
9. **INVESTIGATIONAL THERAPIES** It has been discovered that a considerably greater proportion of sperm from diabetic males contain nuclear DNA damage, which is linked to decreased fertility and a higher likelihood of miscarriages. It's still unclear how this diabetes-related sperm nDNA damage happens. Along with alterations in testicular metabolite levels and spermatogenic gene expression, the detection of elevated levels of advanced glycation end products (AGEs) and their receptor (RAGE) throughout the male reproductive

tract raises the possibility that glycation plays a crucial part in oxidative stress, which damages the DNA of sperm. Glycation may be a common mechanism for the damage observed in sperm since it is a typical byproduct of life and has been linked to DNA fragmentation in several conditions that appear to be unrelated DNA[33] .

10. MEDICINAL PLANTS:

11. Infertile males in the majority of developing nations are treated with both modern therapy and natural remedies. In undeveloped and underdeveloped nations, traditional medicine frequently serves as the initial therapy option for infertile males due to the restricted availability of orthodox medications. As a result, herbal remedies, particularly in isolated regions of emerging and underdeveloped nations, keep growing despite many of the plants' or natural products' claims lack scientific backing. Certain medicinal plants, such as *Lepidium meyenii, Rupus coreanus, Tribulus terrestres*, Korean red ginseng (Panax ginseng Meyer), *Petasites japonicas, celery (Apium graveolens), Eurycoma longifólia, Pedalium murex Linn., Corchorus depressus Linn., Mucuna pruriens Linn, Astragalus membranaceus, Nigella sativa L., and Crataegus* appear to have yielded promising bioactive pro-drug candidates. *Morinda officinalis, Anacyclus pyrethrum, Phaleria macrocarpa, Fagara tessmannii, Crataegus monogyna, and Cynomorium songaricum* may serve as the foundation for additional molecular, cellular, and clinical research aimed at clarifying their modes of action on the testis[34].
12. **NEUTRACEUTICAL TREATMENT**: Products made from food or food elements that offer health advantages, such as illness prevention and/or treatment, are known as nutraceuticals. Stephen DeFelice, MD, first used the term "nutraceutical" in 1989. It is a mixture of the terms "nutrition" and "pharmaceutical"[35].
13. **QUERCETIN** In addition to improving the suppressed sperm count, motility, and viability in diabetic males, QT treatment improved the sexual behavior levels of males. Compared to diabetic males who were not treated, QT-treated males had considerably higher levels of serum testosterone and penile cyclic guanosine monophosphate. In males with diabetes, QT therapies improved penile oxidative stress indicators. After receiving QT treatment, the diabetic male's injured penile tissues were preserved, according to histopathological analysis[36].
14. **FLAVONOIDS** It's interesting to note that natural products have demonstrated a positive therapeutic effect as possible inhibitors for the treatment of male reproductive system malfunction. Flavonoids are among the many natural compounds that have been thoroughly studied for the treatment of disorders of the male reproductive system, including spermatogenesis, testicular structural disruption, and a fall in sperm quality. According to reports, flavonoids contain antiviral, anti-inflammatory, immune-stimulating, anti-apoptotic, anticarcinogenic, anti-allergic, and antioxidant properties. They are also being researched for the treatment of disorders of the male reproductive system[37].

15. **CURCUMIN** It was discovered that curcumin lessened the negative impacts on oxidative stress, histopathological damage, cellular apoptotic activity, and hormone levels. Additionally, it improved sperm motility, concentration, and quality, reduced the activation of the mitogen-activated protein kinase (MAPK) pathway, and restored the levels of MCP-1, TNF-α, and IL-1β in the reproductive organs. Moreover, curcumin has been demonstrated to decrease LDH-x and LDH activity while increasing mRNA, cytoplasmic Bcl-2, 3β-HSD, 17β-HSD and Nrf2 expression, γ-GCS, and GSH-Px levels, as well as the number of TUNEL-positive cells. Male reproductive capabilities are improved by curcumin's pharmacological actions, which demonstrate how curcumin influences different testicular processes. To increase male fertility, this will be essential[38].
16. **HORMONAL MODULATION** Blood glucose levels were significantly lowered by L. micranthus treatment (45.9% and 84.7% on the 7th and 14th post-treatment days, respectively); diabetic male antioxidant status, testicular microarchitecture, lipid peroxidation, and BCl-2 protein expression were all improved in comparison to the control group. In addition, compared to control, L. micranthus therapy enhanced steroidogenic enzyme activity, steroid hormone levels, and sperm quality. It may be possible that L. micranthus's anti-diabetic and aphrodisiac qualities depend on its capacity to correct the redox imbalance that defines male reproductive failure in diabetes[39].
17. **INSULIN SENSITIVITY** Male reproductive system disruption is a significant consequence of diabetes. One crucial step in spermatogenesis is glucose metabolism. Furthermore, the maintenance of both fundamental cell activity and particular processes, such motility and fertilization capacity in mature sperm, depends on glucose metabolism. Both experimentally produced diabetes and diabetic disease showed that either type 1 or type 2 diabetes may negatively impact male fertility, particularly on sperm quality, including sperm motility, sperm DNA integrity, and seminal plasma components. During spermatogenesis, epigenetic changes are crucial. DNA methylation, histone modifications, nucleosome remodeling, higher-order chromatin reorganization, and noncoding RNAs are all examples of chromatin modifications that are represented by epigenetic control. Environmentally induced epigenetic changes may become permanent in the germline epigenome and potentially affect subsequent generations through epigenetic transgenerational inheritance if spermatogenesis is impacted during the critical developmental window, embryonic gonadal development, and germline differentiation. Epigenetic dysregulation may be transmitted through the male germ line and passed on to multiple generations, increasing the risk of diabetes in offspring. Diabetes may also affect epigenetic alteration during sperm spermatogenesis[40].
18. **ERECTILE DYSFUNCTION** In general, ejaculatory dysfunction refers to any situation where normal physiological ejaculation is not achieved. Among these are retrograde ejaculation (RE), failure to generate an ejaculate, delayed ejaculation (DE), premature ejaculation (PE),

absence of ejaculatory feeling, ejaculatory pain, or decreased ejaculatory force. Understanding the pathophysiological mechanisms underlying ejaculatory dysfunction in diabetes mellitus has aided in the development of medicines for managing this condition, even though its etiology can be complicated and multiple. The majority of our knowledge about its pathophysiology comes from diabetic animal models, but human observational studies have also shed light on significant associative elements that may be involved in diabetic men's ejaculatory dysfunction. Depending on the ejaculatory condition, other co-existing complications of diabetes mellitus, certain metabolic variables, and the requirement for reproductive treatment, these have opened the possibility of more individualized treatment plans for patients. However, low-level evidence, which includes retrospective or cross-sectional studies and small sample-size series, supports the therapy of ejaculatory dysfunction, particularly delayed ejaculation and retrograde ejaculation. [41].

19. **Conclusion**: A multifaceted strategy is required to address the multiple issues that diabetes and its treatment pose to male fertility. It is important to carefully assess the possible reproductive negative effects of diabetes drugs, even if they are necessary for glucose control. In addition to improving general health and lowering the risk of infertility, lifestyle interventions provide an additional means of improving reproductive outcomes. Furthermore, the natural bioactive substances found in medicinal plants and their phytochemicals, which target oxidative stress, hormone control, and testicular regeneration, make them a suitable adjunct or alternative therapy. The significance of integrated, patient-specific therapy models is shown by the promising results of combining various approaches within a structured framework to address male reproductive problems caused by diabetes. To enhance therapeutic results, future research should focus on clarifying the molecular processes underlying these therapies and developing evidence-based recommendations A multigenerational animal model derived from maternal or paternal hyperglycemia and transgenerational epigenetic inheritance may be worth considering in future research to solve these problems.

20. Method

I gathered information on diabetes from reputable sources such as Answer thepublic.com, Google Scholar, PubMed, Lancet, Diabetes Care, and others. These sources provided a review of published literature on topics related to diabetes and its complications such as prevalence, quality of life (QoL) prevention measures, medications, herbal treatment, nutrition, and exercise. Additionally, I consulted articles from publications, periodicals, peer-reviewed journals, newspapers, and open-access resources found through Google Scholar. The review included over thirty publications from 1999 to 2024 that specifically focused on programs, for diabetes.

2.1 Abbreviations and Acronyms

Type 2 diabetes mellitus (T2DM).

Authors and Affiliations

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3.1 Figures and Tables

Positioning Figures and Tables: Place figures and tables at the top and bottom of columns. Avoid placing them in the middle of columns. Large figures and tables may span across both columns. Figure captions should be below the figures; table heads should appear above the tables. Insert figures and tables after they are cited in the text. Use the abbreviation “Fig. 1,” even at the beginning of a sentence.

Table 1. **Table of diabetes medications for the reported effects on male fertility**.

Class of Drug	Common Examples	Reported Effects on Fertility	References
Insulin Therapy	Human insulin analogs	It may indirectly improve fertility by controlling diabetes; no direct adverse effect was reported.	*11.*
Sulfonylureas	Glibenclamide, Glipizide	It can induce oxidative stress affecting sperm quality in some cases.	*12*
Metformin	Metformin	It may have protective effects on sperm DNA but could alter androgen levels.	*13.*
Thiazolidinediones	Pioglitazone, Rosiglitazone	Linked to reduced testosterone and sperm abnormalities in long-term use.	*14.*

Class of Drug	Common Examples	Reported Effects on Fertility	References
DPP-4 Inhibitors	Sitagliptin, Vildagliptin	Limited evidence; some studies suggest neutral or beneficial effects.	*11.*
GLP-1 Agonists	Exenatide, Liraglutide	May indirectly benefit fertility by weight reduction but requires further study.	*15.*
SGLT-2 Inhibitors	Empagliflozin, Dapagliflozin	Minimal direct evidence; potential hormonal impact requires exploration.	*16.*

Table 2: Herbal medication that improves male infertility due to diabetes: **Indian herbal medications have been reported to improve male infertility caused by diabetes.**

Plant Name	Scientific Name	Part Used	Mechanism of Action	Reference
Ashwagandha	*Withania somnifera*	Root	Enhances testosterone levels, reduces oxidative stress, and improves sperm motility and count.	17.
Shilajit	*(Mineral resin)*	Resin	Increases sperm motility and count by regulating oxidative stress and mitochondrial function.	18.
Safed Musli	*Chlorophytum borivilianum*	Root tuber	Improves sperm count and motility; protects against diabetes-induced oxidative damage.	19.
Tulsi	*Ocimum sanctum*	Leaves	Reduces testicular damage from diabetes; enhances sperm count and motility.	20.
Fenugreek	*Trigonella foenum-graecum*	Seeds	Improves testosterone levels, sperm count, and insulin sensitivity in diabetic conditions.	21.
Guduchi	*Tinospora cordifolia*	Stem, Leaves	Reduces oxidative stress and inflammation in diabetic-induced infertility.	22.

Plant Name	Scientific Name	Part Used	Mechanism of Action	Reference
Amla	*Phyllanthus emblica*	Fruit	Improves sperm quality by reducing oxidative damage and improving antioxidant enzyme activity.	23.

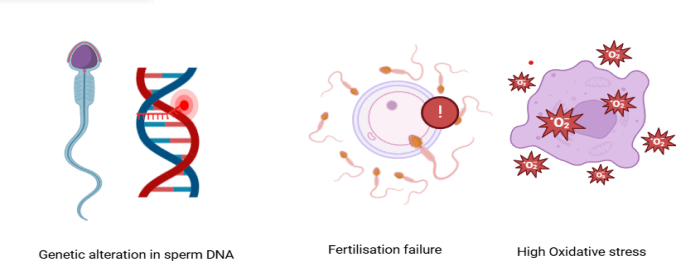

Figure 1. Possible effects of male diabetes on a man's reproductive capacity.

21. Conclusion

A multifaceted strategy is required to address the multiple issues that diabetes and its treatment pose to male fertility. It is important to carefully assess the possible reproductive negative effects of diabetes drugs, even if they are necessary for glucose control. In addition to improving general health and lowering the risk of infertility, lifestyle interventions provide an additional means of improving reproductive outcomes. Furthermore, the natural bioactive substances found in medicinal plants and their phytochemicals, which target oxidative stress, hormone control, and testicular regeneration, make them a suitable adjunct or alternative therapy. The significance of integrated, patient-specific therapy models is shown by the promising results of combining various approaches within a structured framework to address male reproductive problems caused by diabetes. To enhance therapeutic results, future research should focus on clarifying the molecular processes underlying these therapies and developing evidence-based recommendations A multigenerational animal model derived from maternal or paternal hyperglycemia and transgenerational epigenetic inheritance may be worth considering in future research to solve these problems.

Acknowledgment *(HEADING 5)*
The preferred spelling of the word “acknowledgment” in America is without an “e” after the “g.” Avoid the stilted expression “one of us (R. B. G.) thanks ...”. Instead, try “R. B. G. thanks...”. Put sponsor acknowledgments in the unnumbered footnote on the first page.

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