Diabetes mellitus and male infertility

Omolaoye Temidayo S, du Plessis Stefan S

Division of Medical Physiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa

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ABSTRACT

Infertility is prevalent in about 10%-25% of couples in their reproductive age, analogous to 60-80 million infertile couples globally. Of these infertility cases, 10%-30% are exclusively attributed to a problem of the male. Several diseases have been implicated as contributors to deteriorating male fertility and diabetes mellitus (DM) is included. DM, a chronic non-communicable disease, has been considered as one of the most appreciable health threats, as it affects 9% (422 million) of the world’s population as of 2014. It is characterised by hyperglycaemia, which can result from the inability of the pancreatic \( \beta \)-cells to secrete insulin or from the target tissue becoming insensitive to insulin. DM has been reported to influence male reproductive function through diverse pathways and mechanisms. The adverse effects of reactive oxygen species and successive development of oxidative stress that occur due to DM have been investigated and implicated by several studies. The products of non-enzymatic glycosylation are reported to be widely distributed in the reproductive tract of diabetic men. Additionally, DM has been implicated to impair the processes of male sexual acts. Data reported in this review were extracted from PubMed, Google Scholar, Science Direct and Scopus with diabetes and male infertility as the key search words. In light of the aforementioned, the aim of this review is to provide brief background information on DM as well highlight and explain the likely mechanisms of male fertility which DM impacts.

1. Introduction

Diabetes mellitus (DM) is an embodiment of diverse metabolic disorders marked by chronic hyperglycaemia that can result from lack in insulin synthesis and secretion or reduced sensitivity of tissues to insulin[1]. In present day societies, DM represents one of the most noticeable health perils and its prevalence is increasing swiftly. In 2014, the World Health Organization reported that 422 million people have DM, connoting a 60% global increase relative to 2002[2]. The World Health Organization previously projected that the number will rise to about 300 million by 2025[1].
2. Overview of DM

DM prevalence has increased substantially in the last three decades, and has been ranked to be the 7th cause of death in human race[2]. Hyperglycaemia is a known effect of uncontrolled diabetes and consequently can lead to damage to various systems and tissues, especially the nerves and blood vessels[12]. Diverse pathogenic processes are included in the development of DM ranging from pancreatic β-cells autoimmune destruction with insulin insufficiency to abnormalities that causes resistance to insulin action[13]. The fundamental effect of insulin loss or insulin ineffectiveness on glucose homeostasis is the inefficient uptake and usage of glucose by glucose dependent cells, resulting in hyperglycaemia.

In the healthy state, the presence of insulin causes the stimulation of the glucose transporters (GLUTs), allowing glucose to bind to the extracellular portion of these transporters, which results in the translocation of the protein, thus having rapid glucose diffusion into the cell[14,15]. In DM, due to decreased insulin, there is dysregulation of the processes of glucose metabolism and utilization that concurrently alters the stimulatory effect of insulin on glucose transporter translocation.

The numerous cases of DM fall into two broad categories that are classified as Type I and Type II. In both types of DM, metabolism of carbohydrates, lipids and protein are impaired.

2.1. Type I DM

Out of 422 million people affected by DM globally, 10% is attributed to Type I DM. About 85% of this population are diagnosed before the age of 20 and 15% of the cases are ascribed to adults (30 years old). It is instigated by injury or cellular-controlled autoimmune destruction of the pancreatic β-cells. Heredity, race or ethnicity, age and gender are some of the associated risk factors that play a role in ascertaining the susceptibility of the insulin producing cells to abrasion. It may develop swiftly over a period of a few days or weeks, following this sequence: (1) decreased insulin; (2) elevated usage of fats for energy and for formation of cholesterol by the liver; (3) reduction of the body’s proteins[16].

2.2. Type II DM

The prevalence and incidence of Type II DM is rapidly increasing throughout the world and it accounts for 90%-95% of those with DM. Type II DM was known to be an adult or old age disease. But in the last few decades, its prevalence has increased among youth, which predicts for higher estimate of occurrence in the future. It occurs as a result of decreased perceptivity of target tissues to the metabolic effects of insulin. Type II DM is also described as a ‘contemporary disease’ because it is caused by lifestyle factors, such as diet and obesity. Ethnicity, environmental exposure and socio-economic factors are also evident risk factors. In comparison to Type I DM, it is correlated with elevated plasma insulin concentrations (hyperinsulinemia). This occurs as compensatory feedback by the pancreatic β-cells for reduced sensitivity of marked tissues to the metabolic effects of insulin. The diminished insulin sensitivity debilitates carbohydrate usage and storage, increasing blood glucose and spurring a compensatory increase in insulin secretion.

It was predicted in 2016 that there would be a 71.5% prevalence increase of Type II DM amidst age 20-79 by 2035, including 6.0% in Africa, 7.1% in Europe, 11.3% in Middle East, 12.3% in North America and Caribbean, 8.2% in South and Central America, 9.4% in South East Asia and 8.4% in Western Pacific[17]. Considering the above futuristic prevalence evaluation, DM will affect more men ahead of and amid their reproductive years.
3. Impact of diabetes on male fertility

Diabetes has been substantiated to have adverse effects on both male and female reproductive function[16,18] and its impacts can be seen in increased prevalence of infertility[6,19–21]. About 90% of diabetics experience upheaval in sexual function, including a decrease in libido, impotence and infertility[22]. Furthermore, diabetic men are vulnerable to different sexual problems, though progressive physical disorders and deteriorative psychological response are contributors[23]. Several studies have investigated and reported different pathologies commonly experienced by diabetic men and have also highlighted the subsequent reproductive defects. Some of the extracted findings highlighting the impacts of DM on male reproductive functions in human and animal models were represented in Table 1. Selected mechanisms through which DM impact male reproductive function were summarized in Figure 1.

![Figure 1. Mechanisms through which DM affects male reproductive functions. ↑ = increase, ↓ = decrease.]

**Table 1**

Findings highlighting impact of DM on male reproductive functions in human and animal models.

| Reference | Author          | Year | Numbers | Type | Model       | DM                      | Results                                                      |
|-----------|-----------------|------|---------|------|-------------|-------------------------|--------------------------------------------------------------|
| [24]      | Mallidis et al. | 2007 | 52      | In vivo | Human | Type I/Type II | DM                  | Sperm count                                                  |
| [25]      | Agbaje et al.   | 2007 | 56      | In vivo | Human | Type I       | DM                  | Semen volume, ↑ sperm nDNA fragmentation, ↑ deletion of mtDNA |
| [18]      | American Society| 2009 | 12      | In vivo | Human | Type I       | DM                  | nDNA damage                                                  |
| [26]      | Roessner et al. | 2012 | 45      | In vivo | Human | Type I/Type II | DM                  | ↑ nDNA fragmentation, ↑ lipid peroxidation, ↑ disrupted mitochondria potential |
| [27]      | Sudhindra et al.| 2014 | 103     | In vivo | Human | Type I       | DM                  | motility, ↓ semen volume, ↑ DNA damage                      |
| [28]      | Murray et al.   | 1985 | 91      | In vivo | Rats  | Type I       | DM                  | ↑ Testosterone, ↓ LH, Altered sertoli cells, ↑ abnormal morphology |
| [29]      | Maresch et al.  | 2017 | 26      | In vivo | Mice  | Type I       | DM                  | Normal morphology, ↓ seminiferous tubule diameter, ↑ spermatogenic disruption |
| [30]      | Ballester et al.| 2004 | 44      | In vivo | Rats  | Type I, STZ  | DM                  | Testosterone, ↓ Leydig cells, ↓ FSH, ↓ LH                     |
| [31]      | Shrilatha et al.| 2007 | 24      | In vivo | Mice  | Type I, STZ  | DM                  | nDNA damage, ↓ sperm count                                  |
| [32]      | Vikram et al.   | 2008 | 45      | In vivo | Rats  | Type I, STZ  | DM                  | Testosterone, ↑ lipid peroxidation                           |
| [33]      | Jelodář et al.  | 2009 | 16      | In vivo | Rats  | Type I, Alloxan | DM                  | Leydig cells, ↓ sertoli cells, ↓ seminiferous tubule diameter |
| [34]      | Soudamani et al.| 2009 | 36      | In vivo | Rats  | Type I, STZ  | DM                  | Motility                                                     |
| [35]      | Navarro-Casado et al.| 2010 | 86      | In vivo | Rats  | Type I, STZ  | DM                  | Testosterone, ↓ motility                                    |
| [36]      | Mangoli et al.  | 2013 | 20      | In vivo | Mice  | Type I, STZ  | DM                  | Motility, ↓ viable cells, ↑ abnormal morphology              |

STZ=streptozotocin. ↑ = increase, ↓ = decrease.
3.1. Effects on spermatogenesis: role of endocrine disorder

Under normal circumstances, the hypothalamus releases gonadotropin releasing hormone, thereby stimulating the anterior pituitary to secrete luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH stimulates the Leydig cells to secrete testosterone and dihydrotestosterone, while FSH stimulates the Sertoli cells of seminiferous tubes to assist the process of spermatogenesis.

Unarguably, spermatozoa are capable of using glycolysis and/or oxidative phosphorylation in generating energy. They are as well structured to be capable of using external hexoses (glucose, fructose and mannose), and smaller substrates (lactate, citrate amino acids and lipids) for energy production[30]. Though, spermatozoa are known to secret their own insulin, they are however sensitive to hormonal fluctuations[37]. Therefore, deficiency of insulin or insensitivity to insulin in DM alters the endocrine pathway (negative feedback mechanism), resulting in impaired male reproductive function.

Animal studies on induced hyperglycaemia revealed some adverse effects on male reproductive function relative to altered endocrine control (Table 1). Additionally, decreased Sertoli cell vacuolization[26], decreased sperm production[29,33,38–40], decreased fertility[33,41], alteration of epididymis morphology and density[39], decreased LH, FSH and testosterone serum levels[42,43], decreased number of Leydig and Sertoli cells and decreased number of spermatogonia[33] were observed in induced diabetics. The effects of DM on spermatogenesis have not only been shown in animal models, but have also been shown in men (Table 1).

Furthermore, Ballester et al[30] reported a reduction in Leydig cell number and impaired cell function in streptozocin (STZ) induced mice model of DM. The decreased Leydig cell number linked to the decrease in serum LH, which in part explained the stimulatory effects of LH on Leydig cells. This also indicated that the Leydig cells production involving insulin and insulin-like growth factor 1 signal mechanisms is mediated by LH[44,45]. While the impaired cell function was measured by the loss of tyrosine phosphorylation, as well as decreased expression of GLUT-3 receptors, androgen receptors and insulin-like growth factor 1 receptors[36]. These findings are supported by several other animal studies that investigated the effect of DM on male fertility[35,39,46,47]. Also, DM alters spermatogenesis through an FSH-related mechanism. Insulin deficiency present in Type 1 DM does not appear to affect spermatogenesis through a direct effect on the epithelium of seminiferous tubules, but instead by an alteration in serum FSH levels[30,48]. Decreased FSH is followed by a reduction in tubular FSH receptors in STZ induced Type 1 DM, thus causing a diminished response of the epithelium of the seminiferous tubules to FSH stimulation. Therefore, DM alters spermatogenesis by disrupting the modulating effect of insulin on the regulation of serum FSH levels[30,48].

Likewise, glucose has been shown to be important for spermatogenesis and the acrosome reaction (AR). This was evidenced when a medium deprived of glucose inhibited the spontaneous AR, which was swiftly restored after the subsequent addition of glucose[49]. These substrates are conveyed into the cell by GLUTs[50]. GLUTs are specific transporters that catalyze the passive diffusion of glucose into the mammalian cells along a concentration gradient. The GLUT family consists of 14 members and can be divided into three groups based on their sequence similarities[51].

GLUT8 belongs to the class 3 transporters and is expressed predominantly in the testis[52,53]. Research on GLUT8 expression in human spermatozoa revealed its presence in the acrosome and midpiece region of mature spermatozoa[54]. It was also found in the acrosome and midpiece region of mouse mature spermatozoa[55]. While some researches detected GLUT8 in differentiating spermatocytes of the stage 1 type, but not in mature spermatozoa[52]. Glucose transported into the cell is converted to energy, which is needed for spermatogenesis and motility. The disruption of GLUT8 activity caused by decreased insulin resulted in reduced sperm motility and impaired fertilization[56]. This can as well be a result of lower gonadotropin response to gonadotropin releasing hormone in diabetics[44].

3.2. Effect on sperm parameters: role of oxidative stress (OS) and AGEs

Studies have shown that DM induces subtle molecular changes that are essential for sperm quality and function. In a study carried out on 52 diabetic men, semen analysis revealed a significant decrease in sperm motility, including the number of rapid progressive cells[57]. Furthermore, in a comparative study on sperm cryopreservation, semen samples collected from diabetic men showed a significant decrease in sperm parameters when compared to groups of men with autoimmune disorders, kidney diseases, ulcerative colitis and heart diseases[58]. Another study on prevalence of infertility carried out by Delfino et al[59], revealed a significant alteration in sperm kinetic properties and sperm morphology of male diabetic partners. A few more studies also revealed a significant decrease in semen volume, sperm motility and morphology in the semen of diabetic men[25,59]. All these outcomes are associated to the development of OS.

Effect of DM on male reproductive function can also be explained through the impact of OS, caused by the inequality between reactive oxygen species (ROS) production and antioxidant defence mechanisms[60]. The main origins of ROS in the male reproductive system are known to be the immature spermatozoa and leukocytes[60,61]. Additionally, mechanisms that involve repeated mild changes in cellular metabolism may result in tissue damage within a brief occurrence of hyperglycaemia. An enormous bulk of data give priority to certain metabolic pathways as being dominant contributors to hyperglycaemic induced cell damage, e.g., elevated glycolysis, glucose autoxidation, increased polyol pathway flux, increased AGE formation, activation of protein kinase C isoforms and increased hexosamine pathway flux[62,63]. It has been shown that excessive production of O2− by mitochondria in hyperglycaemia is the trigger propel these pathways. Excessive production of O2− momentarily inhibits glyceraldehyde-3-phosphate dehydrogenase activity, which in turn activates all the pathways of hyperglycaemic
damage by diverting upstream glycolytic metabolites to these pathways[62]. Furthermore, when the highly potent ROS exceed the seminal antioxidant defence ability, many cascades of reactions will occur, which can lead to sperm DNA damage and mitochondrial DNA fragmentation, then altered sperm parameters and subsequently male infertility.

In OS, there is excessive production of NO which is detrimental to sperm motility. NO may react with O₂⁻ or H₂O₂ to form ONOO⁻ or OH·, which will cause oxidation of sperm membrane lipids and thiol proteins[45]. It can also cause a decreased ATP levels, thereby affecting the kinematics of spermatozoon.

The high polyunsaturated fatty acids contents in the sperm plasma membrane are susceptible to ROS, its invasion thereof, leads to lipid peroxidation[64]. Lipid peroxidation occurs in 3 stages that are initiation, propagation, and termination. During initiation, free radicals react with fatty acid chains to form the lipid peroxy radical. Peroxyl radicals in turn react with fatty acids to produce free radicals and the reaction is thus propagated. In termination, the two radicals react with each other which lead to lipid break down[64]. Furthermore, oxidation of sugar by OH has been shown to be the main cause of DNA strand breaks. Oxidative damage can further cause base degradation, DNA fragmentation, and cross-linking of proteins. The proportion of DNA strand break is increased in the sperm of infertile diabetic men[9]. Apoptosis, also regarded as programmed cell death, can be instigated by ROS-induced oxidative damage. High levels of ROS alter integrity of mitochondrial membrane[65-68], resulting in mitochondria DNA (mtDNA) damage and subsequently affects sperm functions negatively.

Elevated ROS production has also been implicated in the generation of AGEs. AGEs are products of non-enzymatic reaction between sugar and the amino groups of proteins, lipids and DNA under hyperglycaemic conditions[69,70]. AGEs can alter the normal functioning of macromolecules directly, by generating ROS independently, or indirectly, by activating the receptors for advanced glycation end products (RAGE)[71]. AGEs may play a key role in instigating harm and further act as mediator of damage to reproductive system of diabetic men[72].

RAGE is a ligand binding receptor that increases cellular dysfunction in inflammatory disorders such as DM. RAGE is expressed at low levels in normal tissues. However, in diseased conditions such as DM, its increased expression leads to tissue damage[73,74]. Immunohistochemistry on the testes, epididymis and spermatozoa of 21 diabetic men revealed the wide distribution of RAGE in their reproductive tracts as compared to non-diabetics[24]. An increased prevalence of immunoreactive cells was revealed in the seminiferous epithelium in the testes of diabetic men and sections of the epididymis displayed various degrees of RAGE immunoreactivity. Increased RAGE expression was also found in the spermatozoa acrosomal cap of these men, as determination of the specific location of RAGE was examined during different stages of the AR[72]. It therefore suggests a major role for glycation processes in sperm nDNA damage and cellular damage[24,72].

Furthermore, it has been shown that seminal plasma has important antioxidant systems that can supply the spermatozoa with a defensive environment against OS[45]. However, it was demonstrated that diabetic men have significantly lower seminal total antioxidant capacity (TAC) levels compared to their non-diabetic counterparts. This was supported by another study that showed that seminal TAC has an effect on male fertility and that increased ROS levels leads to low TAC levels[75]. The reduced TAC level in DM is consistent with higher malonaldehyde levels, which suggests a possible role for AGEs in instigating lipid peroxidation levels.

3.3. Diabetic neuropathy

DN is one of the most prevalent complications of DM. It has been reported to affect about 50% of patients with Type I and Type II DM. It can be categorized into autonomic neuropathy and peripheral neuropathy because of its effect on either autonomic or peripheral nervous systems. Both neuropathies results from microvascular dysfunction which can affect the autonomic nervous system (ANS), leading to autonomic neuropathy and can as well impair peripheral nerves causing peripheral neuropathy. Various pathogenic pathways involved in the development of DN and subsequent damage of the male reproductive function were summarized in Figure 2. Since the ANS is involved in the regulation of sexual response cycle, impairment thereof by DN can result in reduced sexual response, erectile dysfunction (ED) and retrograde ejaculation[76].

![Diabetic neuropathy](image)

**Figure 2.** Pathogenic pathways of DN leading to male reproductive function impairment.

NAD=nicotinamide adenine dinucleotide; NADH= reduced nicotinamide adenine dinucleotide; PKC= Protein kinase C. ↑ = increase, ↓ = decrease.
3.3.1. Reduced sexual response
Male sexual response is a result of physical or psychological stimulation which leads to vasodilation and subsequent increased blood flow into the penis. Low libido has been reported to be associated with DM and that it worsens with progressive diabetic state[77]. The reduced sexual response/libido can be related to the physical and psychological susceptibility to deterioration in DM. For instance, Fairburn et al[77] reported an absence of pumping sensation that usually follow ejaculation in over a third of diabetic subjects in their study, with these patients describing semen flowing from their erect or drooping penis’ either at or prior to orgasm.

3.3.2. ED
ED is rampant in millions of men, and has been reported to be more prevalent amongst diabetic men. However, ED’s prevalence depends on variant factors, such as the population reviewed, as well as the definition and methods used[78]. For instance, it was reported that 41.3% of adult men (above 18 years old) in France have ED, 33.2% in Brazil and 41.8% in China[79]; 18.0%-48.0% amongst middle-aged men in Germany[80] and about 50.0% of aging diabetic men (aged 56-85) have ED in the United States[81].

Usually, neurotransmitters, especially NO are released either from the penile nerve endings or endothelium during normal sexual activity, which triggers the relaxation of the cavernosa arteries and the surrounding smooth muscles. This in turn, promotes an increase in penile arterial blood flow, thereby causing an erection. However, diabetic men have impairment in both endothelium dependent smooth muscles and autonomic mechanism that mediate the relaxation of corpora cavernosa[37]. In addition, endothelial dysfunction reflects the loss of NO activity and biosynthesis at the endothelial level, thus leading to ED[82,83].

3.3.3. Retrograde ejaculation
The emptying of semen in the prostatic urethra results in various reflex actions controlled by sensory nerves from the prostatic urethra. This excites centres in the sacral and lumbar regions of the spinal cord, which then transmits impulses to autonomic and somatic pathways, thereby causing ejaculation. However in DM, retrograde ejaculation occurs due to ANS impairment and subsequent loss of constriction by the external urethral sphincter and loss of other reflex actions involved in ejaculation. Retrograde ejaculation can be defined as the retro-influx of semen into the bladder rather than emptying into the anterior urethra[84]. This can result in the subject experiencing the pumping sensation associated with ejaculation without semen emerging from the penis. Urine collected immediately after ejaculation in these men appears cloudy and the diagnosis of retrograde ejaculation can be confirmed by the numerous spermatozoa in a post-orgasmic urine sample.

4. Treatment of male infertility caused by diabetes

Once an individual has been identified as having fertility related issues due to diabetic complications, treatment should be aimed at treating the disease through amelioration of the underlying cause and subsequently treating the consequences.

4.1. Treatment of diabetes
Treatment of DM focuses on controlling the blood glucose levels without causing hypoglycaemia.

4.1.1. Treating Type 1 DM
Effective treatment of Type 1 DM requires administration of sufficient exogenous insulin to maintain glucose metabolisms and also prevent hyperglycaemia. Insulin present in several forms, such as short acting insulin and protein derivative precipitated insulin. The half-life of short acting insulin is 3-8 h, while that of the protein derivatives is 10-48 h[16]. However, treatment should be given with an individualized pattern.

4.1.2. Treating Type 2 DM
Management of Type 2 DM can be accomplished through a strict adherence to healthy lifestyle, diet control, exercise, weight loss and the use of suitable medication in an attempt to reverse insulin resistance. Examples of prescribed drugs for Type 2 DM are metformin and thiazolidinediones. Metformin works by improving the sensitivity of the body tissues to insulin. Thiazolidinediones make the body’s tissues more sensitive to insulin, while sulfonylureas and meglitinides stimulate the pancreas to secret more insulin.

4.2. Treating the consequences

4.2.1. Antioxidant therapy
Antioxidants operate by arresting the oxidative chain reaction, removing, or reducing the formation of ROS[85]. Hughes et al[86] reported a significant protection of a media containing ascorbic acid (600 μmol/L), alpha-tocopherol (30 and 60 μmol/L), and urate (400 μmol/L) from sperm DNA damage by the non-enzymatic antioxidants during an in vitro fertilization (IVF) procedure. Studies on antioxidant treatment of OS related male infertility reported an improvement of the sperm quality and greater assisted reproductive technology (ART) procedures success rate[87-90], but antioxidant therapy still remains highly debated and controversial.

4.2.2. ART
Infertility can be reduced in diabetic men with ED or retrograde ejaculation through intra cytoplasmic sperm injection (ICSI) or IVF. Spermatozoa of diabetic men with ED can be obtained via testicular biopsy. Since ICSI-IVF requires at least one sperm, the sperm retrieved can be injected into the female gamete for fertilization. The fertilized embryo can then be transferred inside the uterus.

Also, ICSI-IVF can as well be applied to treatment of diabetic men with retrograde ejaculation. This can be achieved by recovering the spermatozoa from the post ejaculatory urine of these men. Nakoletlos et al[54] advised that retrograde ejaculation resistant to long term medication can be managed using the ART, following an outcome of 51.2% fertilization rate amongst their study subjects.
4.2.3. Treating diabetic neuropathy

The aim of managing reduced sexual response, ED and retrograde ejaculation, is to help reduce infertility and also aid the affected to enjoy their sexual activities irrespective of the limits set by the diseased. The treatment can be focused on physical, psychological and surgical treatment as well as medication. Physical treatment improves the subject’s general state of health by changing any reversible physical activity contributing to the sexual problem. Psychological treatment is that primary and secondary psychological reactions contributing to the problem should be tackled. Surgical treatment means surgical management of ED includes implantation of penile prostheses and penile vascular regeneration. Surgical procedure to correct retrograde ejaculation can be done by reconstructing the bladder vesical sphincter[91]. Medication refers to drugs commonly used to manage ED that are Avanafil (Stendra), Sildenafil (Viagra), Tadalafil (Cialis) and Vardenafil (Levitra, Staxyn). All these work by relaxing the smooth muscles and boosting vasodilation, thereby making it easier to achieve and maintain erection.

5. Conclusion

DM has been implicated in the impairment of male fertility. Studies have revealed the different mechanisms involved in this pathology. The mechanisms include endocrine disorder, alteration in GLUT8 activity, OS development, AGEs formation and occurrence of DN. It is important that endocrinologists and physicians educate their patients on the possible impact of DM on male fertility, while reproductive endocrinologists should carefully consider the impact of DM as part of their strategies for fertility treatment.

Conflict of interest statement

The authors declare that they don’t have any conflict of interest.

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