

# Not only a matter of glucose: The andrological consequences of diabetes mellitus

Diabetes mellitus (DM) is one of the most frequent noncommunicable chronic diseases worldwide. Although DM is known to increase overall mortality rate, causing 1.5 millions death in 2019,<sup>1</sup> its role on andrological fields is still complex and not completely unraveled. This special issue provides a comprehensive overview of the andrological complications of DM.

## 1 | DIABETIC METABOLIC DYSREGULATION AND HYPOGONADISM

Several lines of evidence, either pre-clinical or clinical, indicate the strong correlation between DM-related metabolic derangements and the reduction in serum testosterone levels.<sup>2</sup> In this setting, Liu et al. suggested the clinical relevance of the triglyceride–glucose index as a marker of both insulin resistance and testosterone decline, using the National Health and Nutrition Examination Survey (NHANES) 2013–2014 and 2015–2016.<sup>3</sup> The relationship is likely to be bidirectional. The impact of T on metabolic parameters is confirmed by data showing that testosterone replacement therapy can improve body composition, metabolic profile, and insulin resistance.<sup>2</sup> On the other hand, antidiabetic drugs cause negligible improvement on circulating testosterone, if any. However, promising results are available on the effectiveness of newer incretin-based agents treating functional hypogonadism.<sup>4</sup> Besides medications, several studies confirm that weight loss by dieting or physical activity is able to improve both metabolic profile and testosterone serum levels.<sup>5</sup> Both metabolic surgery<sup>6</sup> and ketogenic diet<sup>7</sup> could improve testosterone serum levels alongside body weight reduction and metabolic homeostasis improvement. The rapid body weight reduction after very low caloric ketogenic diet is associated with a prompt amelioration of serum testosterone levels, especially in hypogonadal subjects.<sup>8</sup>

## 2 | DIABETIC METABOLIC DYSREGULATION AND SEXUAL FUNCTION

Among sexual dysfunction, erectile dysfunction (ED) is known to be associated with DM, with an estimated prevalence of 52.5% diabetic men among those reporting ED. Although phosphodiesterase type 5 inhibitors (PDE5i) remain the gold-standard treatment for ED,

diabetic men may be less responsive to these drugs. The mechanisms of the reduced PDE5i effectiveness in diabetic men have been summarized by Swiecicka-Mitsides.<sup>9</sup> The limited possibility to use successfully PDE5i requires the identification of alternative treatment strategies. Cayetano-Alcaraz et al. comprehensively reviewed available management options in diabetic patients not-responding to PDE5i.<sup>10</sup> Thus, innovative therapeutical approaches have been developed to improve the ED management in diabetic men. In this setting, the potential therapeutic role of low-intensity extracorporeal shockwave therapy (Li-ESWT) is suggested. Mason et al. systematically reviewed animal and clinical studies related to the use of Li-ESWT for treatment of DM-related ED.<sup>11</sup> Here, Li-ESWT is confirmed to be a safe and effective treatment in men with well-controlled DM and ED.<sup>11</sup>

Alongside from ED-related drugs/interventions, Defeudis et al. comprehensively reviewed the relationship between ED and both diet and antihyperglycemic drugs.<sup>12</sup> A beneficial effect has been described for all drug classes considered, although many antihyperglycemic drugs currently used are still poorly evaluated in this setting and further evidence is needed to draw conclusions.<sup>12</sup> In this regard, Sun et al. confirmed that saxagliptin could alleviate DM-related ED, stromal cell-derived factor-1, and PI3K/AKT pathway.<sup>13</sup>

The discovery of new molecules able to predict ED in DM subjects could open future innovative treatment options. For example, Ragab et al. demonstrated in a proper-designed clinical trial that nesfatin-1 should be considered a biomarker of ED severity in DM subjects, particularly considering the anxiety typical of ED in DM.<sup>14</sup> However, animal models could provide extremely useful information in the detection of new markers relating DM and ED. Rats models highlighted new molecules, such as Sparc, Lox, Srebf1,<sup>15</sup> and specific genes regulating corpus cavernosum smooth muscle cells development,<sup>16</sup> new biomarkers of ED development in DM. Moreover, animal models and basic science could provide new insights in the effectiveness of new drugs and/or approach to ED. Sun et al. demonstrated that paeonol alleviated ED, inhibiting new inflammatory and apoptotic pathways discovered in animal models.<sup>17</sup> Ock et al. showed that knockdown of insulin-like growth factor-binding protein 5 (IGFBP5) improved erectile function promoting cell proliferation and reducing apoptosis and permeability.<sup>18</sup> Thus, the IGFBP5 local inhibition may provide new strategy for diabetic ED.<sup>18</sup>

DM is also considered a potential risk factor for Peyronie's disease (PD), a fibrosing disorder of the penis resulting in plaque formation and

penile deformity that negatively affect sexual function. Gianazza et al. comprehensively reviewed the literature available investigating DM role in PD pathophysiology, diagnosis, and treatment.<sup>19</sup> The authors confirmed that DM is one of the most common comorbidity observed in PD patients, strongly associated with ED onset and to worse outcomes of PD's treatments.<sup>19</sup> Thus, although the role of DM in PD development is still debated, its impact on treatment outcomes is clearly demonstrated.<sup>19</sup>

Besides ED and PD, it is well-known that ejaculatory dysfunction constitutes important sexual sequelae in diabetic men, affecting until the 50% of the casuistry. Desai et al. provided a wide and comprehensive overview on both epidemiology and pathophysiology of ejaculatory dysfunctions in men with DM, considering premature ejaculation, delayed ejaculation, anejaculation, and retrograde ejaculation.<sup>20</sup>

### 3 | DIABETIC METABOLIC DYSREGULATION AND MALE INFERTILITY

In contrast with the evidence on the hormonal and sexual adverse effects of DM, that on the impact of this highly prevalent chronic disease on fertility is much less consistent. Lotti et al. extensively reviewed the clinical studies, which report the relationship among DM, sperm quality, and fertility outcomes,<sup>21</sup> pointing out not only the adverse effect of DM on fertility but also the increased risk of diabetes among childless men.

### 4 | CONCLUSIONS

DM is an increasingly prevalent chronic disease, which is more and more affecting the younger population. Despite its large diffusion, there is still limited awareness on the andrological consequences. ED is a frequent occurrence in diabetic men, and it could represent a marker of subclinical cardiovascular disease. Nonetheless, it is often not systematically assessed and, when assessed, it is often not successfully treated. Successful therapy should take into account that diabetes is frequently associated with low testosterone levels; in addition, medications and treatment options alternative to PDE5 inhibitors should be considered when the latter are not effective. In a good health-care process, it should be borne in mind that ED is only one of the possible sexual concerns occurring in diabetic men: Ejaculatory disorders and PD may be present and worsen the overall sexual satisfaction. Their recognition and management is necessary to improve sexual health.

The impairment in fertility in diabetic men deserves more research efforts. The conflicting evidence on the adverse impact of DM in male fertility highlights the need for further studies to draw final conclusions.

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