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Review

Diabetes associated with male reproductive system damages: Onset of presentation, pathophysiological mechanisms and drug intervention

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ABSTRACT

Diabetes mellitus (DM) is a major health problem that affects patients' quality of life quality throughout the world due to its many complications. Reproductive dysfunction is one of the major secondary complications in both diabetic animals and human beings. Furthermore, DM has recently broken the age barrier and has been heavily diagnosed in children and young persons of reproductive age. In the past few years, many studies on DM in male reproductive functions in both diabetic men and experimental diabetic animals have been published. It is recognized that sustained hyperglycemia, which impairs reproductive function in diabetic men, is at risk of developing. DM harmfully affects male reproductive functions in multiple areas; these may include spermatogenesis, sperm maturation, fertility capability, penile erection, and ejaculation. Traditional medicine and folklore worldwide have used numerous medicinal plants to manage the diabetic reproductive dysfunction because bioactive phyto-constituents are affluent in many places. Unfortunately, the exact reasons for diabetic male reproductive dysfunction are not completely understood and currently there are no treatments in reproductive medicine specifically for such lesions. The aim of this review is to summarize current research findings of DM on reproductive functions, to elaborate the underlying mechanisms related to these diseases via in vivo and in vitro studies, and to describe the ameliorative effects of medicinal plants or their products. The review findings provide a systematic understanding of DM on the reproductive functions and lay the theoretical foundation for developing the direction of reproductive medicine.

Contents

Abbreviations: Apaf-1, apoptotic protease activating factor-1; IL, intromission latency; ARE, antioxidant response element; INHB, inhibin B; Atg, autophagy-related genes; LH, luteinizing hormone; ABP, androgen-binding protein; LC3, light chain 3; CAT, catalase; ML, mounting latency; DM, diabetes mellitus; MF, mounting frequency; EL, ejaculatory latency; NOX, NADPH oxidase; ED, ejaculation dysfunction; Nrf2, nuclear factor-erythroid2-related factor 2; ET-1, endothelin-1; PEI, post-ejaculatory interval; ER, endoplasmic reticulum; ROS, reactive oxygen species; FSH, follicular stimulating hormone; SD, sexual dysfunction; GnRH, gonadotropin releasing hormone; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; STZ, streptozotocin; GSI, gonadosomatic index; TNF, tumor necrosis factor; H&E, hematoxylin and eosin; TF, transferrin; HPG, hypothalamic pituitary gonadal; T, testosterone; IF, intromission frequency; TEM, transmission electron microscopy.

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1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia which often results from the absolute or relative deficiency in insulin secretion and/or insulin action in the beta cells of pancreas [1]. According to an International Diabetes Federation report, 382 million people were affected by diabetes worldwide in 2013 and the diabetes prevalence is expected to be 522 million by the year 2030 [2]. DM is one of the main stressors in modern public health due to its complications which include retinopathy, neuropathy, nephropathy, cardiovascular diseases, and male infertility [3]. Generally, the great majority of patients with type-1 diabetes are diagnosed before the age of 30 [4]. According to the current survey, type-1 diabetes is growing in European children by 3% annually; and there are worrying numbers of children and adolescent youth are diagnosed with type-2 diabetes [5,6]. This increase in diabetes among young people is a great concern as it might affect the reproductive functions of many more men during their active reproductive age. Clinical evidences [7], experimental models [8], and epidemiological studies [1,9] suggest that DM might target specific organs and systems in the body, commonly aiming at genitals. Moreover, recent studies based on the fertility rates of modern societies reveal that the increase incidence of DM is closely related to a falling birth and in-fertility rates [5]. Similar conclusions were also demonstrated in animal models [10,11]. Diabetes could severely impact reproduction. There are histological damage of the epididymis and testis [12], decreased sperm motility [13], semen volume [14], sperm counts, motility and morphology [13,15], and the disruption of seminiferous tubular morphology [16]. These are DM induced male sexual dysfunctions via decreasing serum levels of luteinizing hormone (LH), follicular stimulating hormone (FSH) [10,17], and testosterone (T). Although numerous medicinal plants have been used for intervention studies on diabetic reproductive dysfunction in various traditional medicines and in folklore worldwide, currently there are no treatments for reproductive medicine specifically tailored for diabetic patients. Thus, the study of DM implications in human health is a challenge to research.

Diabetes and its related reproductive impairments have been widely studied, but the exact mechanisms for the reproductive dysfunction in males are not completely understood. Many studies, both in diabetic men and animal models, indicate that a variety of complex regulatory mechanisms, through the mutual interaction, are involved in diabetic reproductive system damage [18,19]. Some studies focused on the molecular mechanisms of various DM induced reproductive system functional abnormalities in males [18,20]. To explore the pathogenesis of diabetic reproductive system damage and to develop drugs that maintain the quality of life in the affected individuals and to minimize their long-term reproductive complications are popular topics in global medicine and pharmacy research.

The present review summarizes recent research findings on DM effects on the reproductive functions which include sperm quality, histopathology of testis, synthesis and secretion of testosterone, ejaculatory function and fertility in both diabetic men and experimental diabetic animals. This review also summarizes the mechanisms that related to these disease via in vivo and in vitro studies, describes the ameliorative effects of medicinal plants or their products especially on male reproductive dysfunctions for providing a systematically in-depth basis to deepen the understanding for diabetic reproductive damages, and furnishing a theoretical direction for developing drugs to repair diabetic reproductive damage.

2. The performance of diabetic male reproductive damage

2.1. Diabetes and testis tissue damage

The male testes possess two major physiological functions: the secretion of testosterone (T) and the production of sperm [21]. The integrity of testicular morphology is vital for its normal function [22]. The weight of testis, the level of testosterone, and the quantity of sperm are important parameters to reflect the reproductive functions of male animals [12,13].

In streptozotocin (STZ) induced animal model of diabetes, Gonadosomatic index (GSI) and the relative weights of testis, epididymis and seminal vesicles were all significantly lower than those of the other experimental groups. The reduction of such index indicated drastic increased testicular damage [14,23]. However, ultrasonography showed no obvious differences in testicular size, prostate volume, and epididymis head and tail size between diabetic and healthy men. But diabetic men had significantly higher levels seminal vesicle gland anteroposterior diameter [18]. Hematoxylin and eosin (HE) staining showed that diabetes evoked malignant histopathological changes in seminiferous tubules via a reduction in the size of the seminiferous tubules, and degeneration and vacuolization in spermatogonia, spermatocytes, and spermatids [23,24]. Also, numerous vacuoles spread around testicular cells with various degrees of spermatogenetic arrest. Evidence indicated an increase in mitochondrial glucose oxidation induced by hyperglycemia in releasing a huge amount of superoxide and other free radicals into the cytoplasm [25]. However, germ cells were vulnerable to oxidation by free radicals which ultimately resulted in testicular tissue damage. Transmission electron microscopy (TEM) showed that spermatogenic cells and sertoli cells displayed severe impairment of organelles through vacuolated mitochondrion and extended endoplasmic reticulum. Nuclear lysis and nuclear membrane invagination accompanied ambiguous boundary was also noticeable [20,22].