Review Article

Diabetes and Male Reproductive Function

LUIS J. RODRIGUEZ-RIGAU

From the Department of Reproductive Medicine and Biology, The University of Texas Medical School at Houston, Houston, Texas

Diabetes mellitus has been known for many decades to be often associated with sexual dysfunction in men (Von Noorden, 1903; Naunyn, 1906). Impotence is by far the most frequent problem, occurring in 37 to 55% of diabetic men (Rubin and Babbot, 1958; Schoffling et al, 1963; Sprague, 1963; Irisawa et al, 1966; Antonini and Petruzzi, 1970; Kolodny et al, 1974; Schneider and Politzer, 1975; Spellacy, 1976; Morley and Melmed, 1979). The incidence of impotence in diabetic men is two to five times higher than in nondiabetic men (Rubin and Babbot, 1958; Schoffling et al, 1963). Diabetes also has been reported to be associated with retrograde ejaculation (Klebanow and MacLeod, 1960; Greene et al, 1963; Ellenberg and Weber, 1966; Kolodny et al, 1974), premature ejaculation (Kolodny et al, 1974), decreased libido (Klebanow and MacLeod, 1960), delayed sexual maturation (Wagner et al, 1942), and infertility or compromised semen quality (Klebanow and MacLeod, 1960; Rubin, 1962; Schoffling, 1965; Irisawa et al, 1966; Bartak et al, 1975). However, numerous studies have been published suggesting that libido, semen quality, and fertility are not commonly affected by diabetes in man (Babbot et al, 1958; Ellenberg, 1971; Paz et al, 1977) and that diabetes is not a frequent cause of male infertility (Goldman et al, 1970; Spellacy et al, 1979). This review will attempt to clarify this controversy by analyzing the available information regarding the effects of diabetes mellitus on the various components of the male reproductive system.

Reprint requests: Luis J. Rodriguez-Rigau, M.D., Department of Reproductive Medicine and Biology, The University of Texas Medical School at Houston, P.O. Box 20708, Houston, Texas 77025.

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Diabetic Neuropathy

Penile erection is controlled by the erigens and pudendal nerves, which originate from the spinal cord at the level of the S_2-S_4 vertebrae (Bors and Comarr, 1960). Thus, involvement of the pelvic autonomic nervous system by diabetic neuropathy can result in impotence. An almost invariable association between impotence and bladder dysfunction in diabetic men has been reported (Rundles, 1945; Ellenberg and Weber, 1967; Ellenberg, 1971; Faerman et al, 1972). This finding was interpreted as suggestive evidence for frequent neurogenic origin of impotence in diabetic men because erection and bladder function are controlled by the same nerves and spinal cord centers (Bors and Comarr, 1960). Ellenberg (1971) in a survey of 200 diabetic men reported a 59% incidence of impotence; diabetic neuropathy was detected in 88% of the impotent men, but in only 12% of the men with apparently normal potency. Faerman et al (1974) reported thickening and beading of penile nerves in diabetic men.

The pelvic sympathetic nervous system responsible for closure of the bladder neck at the time of ejaculation can also be affected by diabetic neuropathy (Odel et al, 1955), resulting in retrograde ejaculation (Greene et al, 1963; Ellenberg and Weber, 1966; Bourne et al, 1971). This abnormality can have a gradual onset, with partial retrograde ejaculation occurring initially (Ellenberg and Weber, 1966), possibly explaining the finding of decreased semen volume in some diabetic men (Klebanow and MacLeod, 1960; Rubin, 1962).

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Faerman et al (1972) observed similarities in testicular histology of diabetic and paraplegic men and suggested that neurologic involvement could be responsible for decreased spermatogenesis in some diabetic men. This hypothesis is supported by reports of disturbance of the germinal epithelium after sympathectomy or excision of the rectum in men (Goligher, 1951; Kim et al, 1966), and by the demonstration that similar testicular lesions can be induced in guinea pigs by section or chemical injury of the sympathetic innervation of the testes (Champy et al, 1952; Coujard, 1952 and 1958). The mechanisms by which a neurologic lesion could damage the germinal epithelium remain to be elucidated.

Diabetic Vascular Disease

Several reports have indicated that diabetic men frequently have small vessel lesions with calcification of scrotal vessels (Wilson and Markus, 1951; Klebanow and MacLeod, 1960) and may also have decreased penile blood pressure and blood flow (Abelson, 1975). Thus, vascular complications of diabetes could be responsible for impotence and testicular dysfunction.

Diabetes and the Hypothalamic–Pituitary–Testicular Axis

Androgen Production

Wagner et al (1942) reported that diabetic boys frequently have delayed sexual development. Decreased excretion of 17-ketosteroids in diabetic men was reported shortly thereafter (Miller and Mason, 1945). Schoffling et al (1963) noted a decreased number of Leydig cells in testicular biopsies of diabetic men. These reports were interpreted as evidence that diabetes results in decreased androgen production in man, and Schoffling et al (1965) advocated replacement therapy with testosterone for impotence in diabetic men.

On the other hand, the association of diabetes mellitus with Leydig cell dysfunction in man has been disputed by many investigators. Both plasma testosterone levels and excretion of 17-ketosteroids have been reported to be within normal range in diabetic men and to not correlate with impotence (Rivarola et al, 1970; Ellenberg, 1971; Faerman et al, 1972; Kolodny et al, 1974; Paz et al, 1977). Light and electron microscopic examination of testicular tissue has disclosed that both the number and the morphologic characteristics of interstitial cells were normal in impotent as well as nonimpotent diabetic men (Warren et al, 1966; Rivarola et al, 1970; Faerman et al, 1972). Schneider and Politzer (1975) were unable to demonstrate a significant correlation between plasma testosterone levels and impotence in diabetic men. Faerman et al (1972) reported normal basal and hCG-stimulated plasma testosterone levels and normal testicular metabolism of ^{3}H-pregnenolone *in vitro* in diabetic men. Testosterone has been observed to be ineffective in the treatment of impotence in diabetic men (Ellenberg, 1971), although no controlled studies of its effectiveness have been published.

Studies in laboratory animals appear to support the hypothesis that diabetes exerts a detrimental effect on Leydig cell function. In immature rats, alloxan-induced diabetes has been reported to retard or suppress sexual development (Chesler and Tislowitz, 1945; Hunt and Bailey, 1961). In rats with diabetes induced by subtotal pancreatectomy, sexual behavior was decreased, accessory reproductive glands were atrophic, and testicular testosterone synthesis *in vitro* was suppressed (Foglia et al, 1963 and 1969). These disturbances increased in severity as the duration and the degree of hyperglycemia increased. In prediabetic rats (shortly after partial pancreatectomy, when blood glucose levels were below 120 mg/dl) no disturbances of testicular function were observed (Foglia et al, 1969). These results suggest that the suppression of androgen production induced by diabetes may be related to the degree and duration of hyperglycemia. A reduction in both Leydig cell number and testosterone secretion was observed also in rats with streptozotocin-induced diabetes (Paz et al, 1978).

Since most relevant clinical studies published to date were conducted without regard to the degree of control of blood glucose levels, the possible effect of diabetes mellitus on testicular androgen production needs to be evaluated by properly designed and controlled studies. In addition, since it has been suggested that certain antidiabetic agents such as sulfonylureas exert a direct inhibitory action on testicular testosterone production (Shahwan et al, 1978), not only the status of the glycemia in each patient but also the type of therapy would have to be considered in such studies. Finally, some reports suggested decreased

sex-hormone binding globulin capacity in diabetic men (Wright, 1976) and increased excretion of estrogens in impotent as compared to potent diabetic men (Krese, 1966). Additional studies will be required to confirm these findings and uncover their pathophysiologic mechanisms.

Gonadotropin Secretion

Reports of urinary and blood gonadotropin levels in diabetic men have been as contradictory as were the reports concerning androgen levels (Bergquitst, 1954; Schoffling et al, 1963; Schoffling, 1965; Rastogi et al, 1974; Distiller et al, 1975; Paz et al, 1977). On the basis of observation of decreased urinary gonadotropins in impotent diabetic men, Schoffling (1965) suggested a relationship between diabetes and hypogonadotropic hypogonadism. This relationship was disputed by other investigators, since both basal and GnRH-stimulated blood gonadotropin levels were found to be normal in diabetic men (Rastogi et al, 1974; Paz, 1977). Distiller et al (1975), in what is probably the most useful study to date, demonstrated a blunted gonadotropin response to GnRH in men with improperly controlled diabetes, and reported a statistically significant inverse correlation between the maximum levels of luteinizing hormone (LH) after GnRH and the blood glucose levels during fasting. Wright (1976) confirmed the blunted LH response to GnRH in diabetic subjects. Thus, it appears that there is a relation between the degree and possibly the duration of hyperglycemia and anterior pituitary function (gonadotropin secretion) in diabetic men. This could be responsible for the similar relation between hyperglycemia and androgen production discussed in the previous section of this review. Again, it seems clear that the conclusions from studies carried out without regard to the degree of control of glycemia in the diabetic subjects may be invalid, as emphasized recently by Spellacy (1976).

The recent results concerning the relationship of diabetes and gonadotropin secretion in men appear to be supported by the results of studies in experimental animals. Reduced gonadotropic secretion and histologic lesions in the anterior pituitary have been reported to occur in diabetic rats (Soulairac and Desclaux, 1948; Paz et al, 1978; Foglia et al, 1969). Godner and Freinkel (1961) demonstrated that the uptake of glucose by the anterior pituitary of normal and diabetic rats is enhanced by insulin *in vitro*. Dixit and Lazarow (1961) reported accumulation of glycogen in the anterior pituitary of diabetic rats and of normal rats treated with glucose, and reversal of these changes after insulin administration. Thus, it appears that the anterior pituitary, like other tissues, is dependent upon insulin for normal utilization of glucose. An insulinopenic state may cause reduced gonadotropin secretion as the result of a general impairment in pituitary protein synthesis (Morley and Melmed, 1979).

Finally, the results of an investigation by Moguilevsky et al (1966) suggested that the effect of hyperglycemia or insulinopenia on gonadotropin secretion of diabetic animals could be mediated by effects on the hypothalamus. In support of this possibility, Paz et al (1978) observed normal pituitary response to luteinizing hormone–releasing hormone (LH–RH) in streptozotocin-treated diabetic rats in which peripheral LH levels were significantly reduced. These authors concluded that experimentally induced diabetes interferes with secretion of LH–RH.

Diabetes and Spermatogenesis

Studies undertaken either before insulin was available or during the early years of insulin use suggested the association of diabetes with testicular atrophy in men (Koch, 1910; Kraus, 1923). Since then, a number of contradictory reports have been published, some suggesting association of diabetes to lesions of the germinal epithelium, oligospermia, and infertility (Rubin, 1962; Schoffling et al, 1963; Villanueva et al, 1964; Schoffling, 1965; Irisawa et al, 1966; Faerman et al, 1972) and others claiming no detrimental effect of diabetes on fertility (Babbot et al, 1958) or sperm count (Klebanow and MacLeod, 1960; Ellenberg, 1971; Bartak et al, 1975; Paz et al, 1977). In fact, some investigators reported higher sperm counts in diabetic men than in control subjects (Klebanow and MacLeod, 1960). Warren et al (1966) suggested that the germinal epithelium lesions observed by earlier investigators were secondary to malnutrition, weakness, or general nonspecific effects of the disease. Faerman et al (1972) reported that in impotent diabetic men the wall of the testicular seminiferous tubules was of normal thickness and had no fibrosis or hyalinization. However, some degree of hyposper-

matogenesis with sloughing of the germinal epithelium was observed.

Animal studies suggest a detrimental effect of diabetes on male reproductive function. Testicular lesions have been described in the dog, cat, cock, hamster, and rat with alloxan-induced or spontaneous diabetes; these lesions are partially reversed by insulin administration (Chesler and Tislowitz, 1945; Soulairac and Desclaux, 1948; Foglia et al, 1963; Schoffling et al, 1967; Foglia et al, 1969). It was speculated that the effect of diabetes on testicular histology could be due either to decreased function of the hypothalamic–pituitary–testicular axis, or to a direct effect of hyperglycemia on the testis (Foglia et al, 1969).

In order to investigate the incidence of diabetes in oligospermic men, Goldman et al (1970) performed oral glucose tolerance tests (GTTs) and prednisone-stressed GTTs in 15 men who had sperm counts below 20 million/ml and 15 men with sperm counts greater than 50 million/ml. No differences were found. In a similar study, Spellacy et al (1979) subjected 27 male partners of infertile couples to 3-hour GTTs. No significant differences in glucose or insulin curves were found when men with sperm counts below and above 20 million/ml were compared. Moreover, similar sperm counts were observed in men with normal and abnormal responses to the GTTs. The authors concluded that a mild abnormality of carbohydrate metabolism usually does not affect male fertility, and that routine evaluation of the carbohydrate metabolic status of every patient with abnormal semen analysis is probably not cost effective.

Diabetes and Sperm Motility

Klebanow and MacLeod (1960) studied semen quality in 19 diabetic men able to ejaculate; 11 of these men were found to have sperm motilities below 50%. Rubin (1962) reported sperm motilities below 30% in eight of 11 diabetic men, and Bartak et al (1975) noted decreased velocities of spermatozoa of 25 diabetic boys when compared to those of spermatozoa from 24 control subjects. However, normal sperm motilities in diabetic men have also been reported (Ellenberg, 1971; Paz et al, 1977).

The mechanism(s) by which diabetes could result in decreased sperm motility have not been elucidated. Povoa et al (1972) and Hicks et al (1973) demonstrated that seminal plasma contains immunoreactive insulin in higher concentration than serum, and suggested a role for insulin in the regulation of sperm metabolism and motility. Addition of insulin was reported to stimulate glucose and pyruvate metabolism by spermatozoa from normal subjects, while it had no effect on fructose utilization (Hicks et al, 1972). When fructose was used as substrate, addition of insulin had no effect on sperm motility, while motility was increased when glucose or pyruvate were used (Hicks et al, 1973). These results were disputed by Paz et al (1977), who were unable to demonstrate an *in-vitro* effect of insulin on glucose utilization, lactate production, or oxygen consumption by washed spermatozoa from normal or diabetic men. In addition, these investigators observed no differences when the sperm motilities of patients with low or high semen insulin levels were compared, and reported that stimulation of semen insulin levels by arginine administration *in vivo* resulted in no change in sperm motility. Thus, they concluded that there was no evidence for an effect of insulin on spermatozoal metabolism or motility.

Decreased sperm motility in diabetic men could also result from low fructose levels, as suggested by Salama-Benarroch (1964). However, this observation has not been confirmed by other authors. Alternatively, diabetes could result in disturbed spermiogenesis and/or abnormal spermatozoal maturation in the testes and epididymides. A slight increase in the frequency of morphologically abnormal spermatozoa in semen from diabetic men has been reported (Bartak et al, 1975). The carbohydrate metabolism of testicular spermatozoa is different from that of ejaculated spermatozoa (Rodriguez-Rigau and Steinberger, in press).

Summary and Conclusions

Diabetes mellitus in man is frequently associated with sexual dysfunction. It is now generally agreed that retrograde ejaculation and impotence in diabetic men are caused in the majority of cases by diabetic neuropathy of the pelvic autonomic nervous system. Occasionally, impotence may be related to diabetic vascular disease. Decreased androgen production is an extremely rare cause of impotence in diabetic men. Thus, testosterone should not be used empirically in the treatment of these patients.

Reports on the effects of diabetes on androgen and gonadotropin secretion, testicular histology, semen quality, and fertility of men have often been contradictory, with some authors suggesting that diabetes results in severe disturbances and others reporting no detrimental effects. This discrepancy appears to be related predominantly to differences between study populations, particularly with regard to the degree of control of the diabetes of each patient and the type of treatment that the subjects received. Recent reports have suggested that the function of the hypothalamic–pituitary–testicular axis remains normal or is only very mildly affected in patients with well-controlled diabetes, while suppression of gonadotropin and androgen secretion and testicular lesions occur in patients with improperly controlled diabetes. This conclusion is supported by studies in laboratory animals demonstrating that disturbances of pituitary and testicular function in diabetic animals increase in severity with the duration and degree of hyperglycemia. Thus, the question of the possible effect of diabetes on the hypothalamic–pituitary–testicular axis in man needs to be re-evaluated in properly designed and controlled studies.

Although several reports have been published suggesting the association of diabetes in man with compromised spermatozoal motility, this is also controversial; the mechanisms by which diabetes could result in this disturbance remain to be elucidated.

Finally, it is important to emphasize that the incidence of undiagnosed diabetes in patients with compromised semen quality is very low. Thus, this reviewer agrees with Spellacy et al (1979) that routine evaluation of the carbohydrate metabolic status of every patient with abnormal semen analysis is probably not cost effective.

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