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REVIEW

The Endocrine System in Diabetes Mellitus

Hisham Alrefai,[1] Hisham Allababidi,[1] Shiri Levy,[2] and Joseph Levy[1]

[1]Division of Endocrinology at Wayne State University School of Medicine, Detroit, MI; and [2]William Beaumont Hospital, Detroit, MI

The pathophysiology of diabetes mellitus is complex and not fully understood. However, it emerges as an abnormal metabolic condition associated with a systemic damage to the vascular bed. Cumulative evidence also reveals that the endocrine system is not intact in patients with diabetes mellitus. It is not clear whether the changes observed in the endocrine system represent a primary defect or reflect the effects of the impaired insulin action and abnormal carbohydrate and lipid metabolism on the hormonal milieu. Review of the literature reveals that the function of the entire endocrine system including the functions of hormones from the hypothalamus, pituitary, adrenal, thyroid, parathyroid, the vitamin D system, the gonads, and the endocrine function of the adipose tissue, is impaired. Good metabolic control and insulin treatment may reverse some of these abnormalities.

It remains unanswered as to what extent these changes in the endocrine system contribute to the vascular pathologies observed in individuals affected by diabetes mellitus and whether part of the abnormalities observed in the endocrine system reflect a basic cellular defect in the diabetic syndrome.

Key Words: Diabetes mellitus; type 1; type 2; hormones; pituitary; hypothalamus; adrenal; androgens; thyroid; parathyroid; adipose tissue.

Introduction

Although its etiology is still unclear, diabetes mellitus emerges as an abnormal chronic systemic condition, characterized metabolically by a decrease in insulin action and hyperglycemia. The decrease in insulin action may be secondary to a decrease in insulin secretion, increased insulin resistance, or both. It is associated with a systemic damage to the function of the vasculature, and both the microvascular and macrovascular beds are involved.

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Author to whom all correspondence and reprint requests should be addressed: Professor Joseph Levy, M.D., Division of Endocrinology, Wayne State University School of Medicine, VA Medical Center, 4646 John R Street, Detroit, MI 48201. E-mail: joseph.levy@med.va.gov

Consequently, abnormalities were found in every organ and tissue tested in individuals affected by diabetes. Traditionally, the emphasis was placed mainly on the kidneys, eyes, and peripheral nerves as far as the microvascular bed is concerned and on the heart and peripheral arteries as far as the macrovascular bed is concerned. This is not surprising in view of the major impact that the impairment in these organs have on the morbidity and mortality in diabetes mellitus.

However, a search of the literature reveals that the endocrine system is also not spared in diabetes mellitus. Although more research is needed in order to further explore the abnormalities in the endocrine system observed in diabetes mellitus, it emerges that almost the entire system is not functioning normally in this condition.

Furthermore, there might be an interrelationship between the diabetes condition and the endocrine system. For example, although severe hyperthyroidism may aggravate the impairment in metabolic control in diabetes, severe decompensation of the metabolic control may further impair the thyroid function.

In this review we will summarize, in a systematic manner, most of the described pathologies of the endocrine system seen in both human and experimental diabetes. We will also attempt to evaluate the potential impact of these changes on the pathologies observed in the diabetes condition.

Growth Hormone–Insulinlike Growth Factor Axis

Growth hormone (GH) plays a significant role in protein synthesis, stimulates lipolysis, and antagonizes insulin action. Many of its effects are also mediated by insulinlike growth factor-1 (IGF-1), a potent growth and differentiation factor *(1)*.

In animal diabetes, there is a decrease in the gene expression of the hypothalamic somatostatin and GH-releasing hormone (GHRH) as well as the pituitary GH and GH receptor *(2)*. The circulating levels of growth hormone are suppressed *(3,4)*, with decreased amplitude and duration and reduced frequency of the GH pulses *(5)*.

In humans, poorly controlled type 1 diabetes is associated with high plasma levels of GH and low levels of IGF-1 *(6,7)*. Furthermore, intensive metabolic control does not normalize the increased mean 24-h GH concentration *(8)*. Also,

urinary GH excretion is increased in type 1 diabetics, and the urinary GH concentration correlates with the daily dose of insulin *(9)*. Interestingly, in type 1 diabetes, glucose fails to suppress GH levels and may even raise them paradoxically *(10,11)*. In addition, GH levels may also rise during insulin administration even without concomitant hypoglycemia *(12,13)*.

It has been shown that uncontrolled type 1 diabetics have an exaggerated GH response to exogenous GHRH along with a blunted IGF-1 response *(14)*, suggesting a central hypersensitivity to GHRH and a peripheral resistance to GH. The GH resistance state may be partially explained by the downregulation of hepatic growth hormone receptors (GHR) *(15–18)*. In addition, insulin is needed for hepatic IGF-1 synthesis and secretion *(19)*, and because there is an insufficient portal insulinization in type 1 diabetics, this may contribute to the decreased IGF-1 response. In turn, decreased IGF-1 levels may impair the negative feedback on GH secretion, resulting in high levels of the hormone. Increasing the IGF-1 levels by administration of rh-IGF-1 decreases GH secretory bursts in type 1 diabetics *(20)*.

In poorly controlled type 1 diabetic patients, GH levels fluctuate more with increased daytime pulse frequency and higher amplitude *(8,21)*. Tight metabolic control does not change the amplitude and width of the GH pulses, but does equalize daytime and nighttime pulse frequency *(8)*. Similarly, abnormal pulsatile secretion of GH has also been described in patients with type 2 diabetes *(22),* who have more frequent secretory bursts, but the amplitude of the bursts is smaller than in nondiabetics. These changes may be the result of the commonly associated obesity and correlate with the long-term glycemic control *(22)*.

The IGF-1 level is decreased in type 1 diabetes *(6,7)* and insulin treatment partially reverses this defect *(23)*. Also, the IGF-1 activity is decreased in type 1 diabetes and the level of the activity correlates with the level of the glycemic control *(24)*. Some studies have shown that improved glycemic control may increase IGF-1 levels in type 1 diabetics *(6,25)*, whereas others did not *(26,27)*. Levels of IGF-1 are also decreased in type 2 diabetic patients *(28)*.

Insulin deficiency decreases liver GHR gene expression and GH-binding protein (GHBP) levels. These defects are reversed by insulin administration *(15–18,29)*. GHBP levels are also decreased in patients with type 1 diabetes and patients with type 2 diabetes who have low insulin levels. The levels of GHBP correlate with the degree of the insulinopenia *(30)*.

However, continuous exposure to insulin may also reduce GH binding *(31)*. Insulin is an important inhibitor of hepatic insulinlike growth factor binding protein-1 (IGFBP-1) synthesis and secretion, and IGFBP-1 levels tend to be increased in patients with type 1 diabetes *(32,33)*. The diurnal IGFBP-1 pattern, with increasing concentrations during the night and early morning hours and falling concentrations during daytime, is preserved in type 1 diabetics *(34)*. There is an inverse correlation between IGFBP-1 and insulin levels, whereas hyperglycemia per se does not affect IGFBP-1 levels *(34)*. In type 1 diabetic patients, insulin withdrawal increases IGFBP-1 and IGFBP-3 levels and decreases the free IGF-1 levels *(23)*.

It was proposed that the impairment in the GH–IGF-1 axis might play a role in the pathogenesis and progression of diabetic complications such as retinopathy, microalbuminuria, and diabetic nephropathy *(35)*. Others showed that pharmacological levels of IGF-1 are needed to increase glomerular filtration rate (GFR) and renal plasma flow (RPF) and suggested that the level of alteration in the GH–IGF-1 axis in diabetics is not sufficient to cause an increase in GFR or RPF *(36)*. It was also proposed that IGF-1 might play a role in the pathogenesis of proliferative diabetic retinopathy (PDR). This is supported by various observations, including PDR improvement after hypophysectomy *(37,38),* rarity of PDR in GH-deficient diabetic dwarfs *(39)*, and the high levels of vitreous IGF-1 levels in patients with PDR compared with controls *(40,41)*. Finally, treatment with octreotide may retard the progression of advanced diabetic retinopathy and may delay the initiation of photocoagulation therapy *(42)*.

Hypothalamic–Pituitary–Adrenocortical Axis

Glucocorticoids

Corticotropin-releasing hormone (CRH) secretion is impaired in both animal and human diabetes mellitus. Hypothalamic CRH gene expression is decreased in STZ diabetic rats *(43,44)* and is normalized by treatment with insulin *(43)*. It was suggested that in addition to CRH, other hypothalamic factors activate the hypothalamic–pituitary–adrenal axis in uncontrolled diabetes and inhibit the CRH gene expression indirectly by a negative glucocorticoid feedback *(44)*.

In type 2 diabetic patients, basal serum CRH levels are decreased *(45)* and basal serum adrenocorticotropic hormone (ACTH) levels are increased *(46–48)*. Type 2 diabetes is also associated with an abnormal circadian rhythm of serum ACTH and cortisol *(49,50)*. This increase in plasma ACTH and cortisol in patients with type 2 diabetes is not caused by CRH stimulation *(45)*. In this regard, insulin itself may stimulate the hypothalamic–pituitary–adrenocortical secretory activity in humans at both the peripheral and the central levels of the axis *(51)*.

Diabetes mellitus is associated with hypercortisolism *(52)*. Type 2 diabetic patients have higher fasting serum cortisol levels *(48)*, an exaggerated nocturnal rise in plasma cortisol *(51)*, and elevated 24-h plasma cortisol profiles *(52,53)*. Poor glycemic control may increase cortisol production *(54, 55)*. Type 2 diabetic patients have also diminished suppression of cortisol metabolites in response to dexamethasone *(49,56)*. These changes in cortisol metabolism may contribute to the hypertension, obesity, and menstrual irregularity seen commonly in type 2 diabetes, which are similar to what is seen in Cushing's syndrome.

Patients with type 1 diabetes mellitus have increased 24-h urinary free-cortisol (UFC) excretion, and there is a correlation between the 24-h UFC excretion and the duration of the disease *(57)*. Twenty-four-hour UFC excretion is also higher in diabetic patients with retinopathy or with cardiovascular complications compared with patients without these complications *(57)*.

Tight glycemic control diminishes the response of ACTH and cortisol to hypoglycemia *(58,59)*. This could be caused by a hypothalamic–pituitary adaptation to hypoglycemia rather than by an alteration in the adrenal gland function *(58)*. This phenomenon might be of significance in the treatment of diabetic patients.

Adrenal Androgens

Serum levels of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) are decreased in type 2 diabetic male patients *(60–63)*. It has been shown that the decreased levels of serum DHEA and DHEA-S correlate with an increased incidence of atherosclerosis in men *(63)*. Thus, the decrease in DHEA and DHEA-S levels in type 2 diabetics may contribute to the increased incidence of ischemic heart disease in this population. Poor glycemic control may further decrease DHEA levels *(64)*.

There is a negative correlation between serum insulin levels and DHEA and DHEA-S levels *(65)*. A marked decline in serum DHEA-S levels was observed in normal men and women during experimentally induced hyperinsulinemia irrespective of glycemic level *(62,66)*. Others reported that in male patients with either type 2 diabetes or impaired glucose tolerance (IGT), hyperglycemia induced a decline in both DHEA and DHEA-S and this decline was independent of the serum insulin levels *(60,63)*.

Unlike observations in type 2 diabetes, there is no difference between levels of DHEA-S and androstenedione seen in patients with type 1 diabetes and those seen in their nondiabetic siblings *(67)*. In women with type 2 diabetes, DHEA-S levels are normal or increased *(68,69)*.

Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone system (RAAS) plays an essential role in cardiovascular function and electrolyte balance. Renin release from renal juxtaglomerular cells results in a cascade of events, which ultimately generate angiotensin II. Angiotensin II, in turn, induces systemic and intraglomerular hypertension, increases glomerular capillary permeability, stimulates aldosterone secretion, and promotes production of the presclerotic cytokine transforming growth factor (TGF-β) *(70)*.

The identification of many components of the renin–angiotensin system (RAS) in various organs, including fat tissue *(71,72)*, suggest that this system may also play a role in the regulation of local tissue functions. Furthermore, the intrarenal RAS may act independently of the systemic renin–angiotensin in diabetic patients *(73,74)*, and there is evidence for a role of the renal RAS in the pathogenesis of diabetic nephropathy *(75–77)*.

Studies in animal diabetes suggest that plasma levels of angiotensinogen, angiotensin II, rennin, and aldosterone are unchanged *(78–81)*. However, local renal RAS is activated at early stages, leading to increased local production of angiotensin II *(81)*. Others have found that in type 1 and type 2 human diabetes as well as animal diabetes, plasma renin activity *(80,82–84)* and serum aldosterone levels are decreased *(85,86)*. The hyporeninemic hypoaldosteronemic state in animal and human diabetes has been associated with a variety of conditions, including hypertension, nephropathy, neuropathy with attenuated sympathetic nerve activity, and angiopathy *(87,88)*.

Some investigators have found an increased activity of the renal renin system in animal and type 1 and type 2 human diabetes and have suggested that it might be caused by an autonomous and an unsuppressed local RAAS function *(73, 89–91)*. It is possible that the differences in the described RAS function in diabetes may reflect different phases in the progression of the diabetic state.

At the receptor level, in animal diabetes, angiotensin receptor 1 (AT1) density and angiotensin II binding to its receptor in the glomerulus are decreased *(79,91,92)*. Treatment with insulin reverses this abnormality *(93)*. Myocardial AT receptors *(81,94)*, on the other hand, are increased in diabetes, and this change is less responsive to insulin therapy *(81)*. These findings suggest a differential regulation of the AT receptors in the kidney and heart in diabetes. Finally, at the adrenal level, aldosterone response to angiotensin II is unaltered in type 2 diabetic patients *(73)*.

Taken together it seems that diabetes may result in an initial stage of RAAS hyperactivation, followed by a state of hypo-reninemic hypoaldosteronism at later stages. The increased renal RAS activity in diabetics may explain their favorable response to treatment with angiotensin-converting enzyme inhibitors.

Adrenal Medulla

Adrenal medullary epinephrine secretion plays an important role in the body response to hypoglycemia. When glucose concentration falls below overnight fasting levels, regulatory glucose-sensitive neurons in the central nervous system initiate a prompt increase in adrenal medullary secretion. This increase, which may reach levels of 25–50 times above baseline, increases hepatic glucose output and provides an alternative substrate in the form of free fatty acids, suppressing insulin release and inhibiting insulin-mediated glucose utilization in muscles. Diabetes may affect the adrenal medulla and its function. *(95)*.

Experimental diabetes is associated with an increase in the weight and size of the adrenal medulla and an increase in the adrenal concentration of epinephrine, norepinephrine, and dopamine *(96,97)*.

In type 1 diabetic patients, 24-h urinary epinephrine excretion is increased and this is only partially reversed by improvement in the glycemic control *(98)*. Although the mean daily epinephrine level is increased, the circadian rhythm of its secretion is preserved *(99)*.

Adrenal medullary fibrosis and medullitis were observed in autopsies of patients with type 1 diabetes, and there was an association between the duration of the diabetes and the degree of fibrosis. This medullary fibrosis was not observed in type 2 diabetes *(100,101)*. Circulating anti-adrenal-medullary antibodies were demonstrated in new-onset type 1 diabetic patients *(102)*, even before the onset of the clinical diabetes *(103)*.

Patients who have diabetes for a long time and have autonomic neuropathy may fail to exhibit the physiologic increase in circulating epinephrine levels in response to hypoglycemia *(104)*. This defect, in addition to a defective glucagon response (*105)*, is of significance in the pathogenesis of the hypoglycemia unawareness condition seen in individuals with long-standing type 1 diabetes (*106)*.

Strict glycemic control is associated with a lowering of the threshold of the plasma glucose that triggers epinephrine release *(107)*. In animal diabetes, epinephrine secretion by the adrenal glands in response to a direct electrical stimulation of the splanchnic nerve terminals is severely attenuated *(108)*.

Experimental diabetes is also associated with changes in the physiologic response to catecholamines. A decrease in the adrenergic receptors of the myocardium *(96)* and an enhanced vasoconstrictive effect of catecholamines on the blood vessels were described *(109–111)*. This increased catecholamine vasoconstrictive effect in diabetes was proposed as a potential contributing factor to the increased prevalence of hypertension seen in this condition**.**

The lipolytic response to epinephrine is either increased *(112)* or not affected by diabetes *(113)*.

Hypothalamic–Pituitary–Gonadal Axis in the Male

The major functions of androgens are the formation of male phenotype and induction of sexual maturation and fertility. They also play a role in the anabolic status of somatic tissues. Diabetes may affect androgen metabolism *(114)*.

In diabetic rats, the hypothalamic luteinizing hormone-releasing hormone (LHRH) release has been reported to be intact *(115)* or decreased *(116)*. Physiologically, neither a loss of LHRH neurons in the hypothalamic nuclei nor a decrease in the hypothalamic responsiveness to an adrenergic stimulation has been found *(115,117)*.

Conflicting results have been observed with regard to the ambient gonadotropin hormones levels, and their response to gonadotropin-releasing hormone (GnRH) or to castration ranged from decreased to normal *(118–122)*. The blunted response could be explained, in part, by a defect in the glycoprotein component of the LH receptor as a result of abnormal glucose metabolism in diabetes *(123)*. However, insulin treatment reverses this pituitary defect *(124)*. In human studies, some investigators found no significant abnormalities in gonadotropin secretion in diabetic patients *(125)*. Others reported elevated gonadotropin levels in both type 1 and type 2 diabetic men *(126,127)*. In addition, reports concerning serum testosterone levels in diabetic male rats *(118,119)* and in type 1 and type 2 diabetic men *(125,128–132)* are inconsistent. Some studies showed normal total testosterone levels in type 1 and type 2 diabetic men *(125, 128,129)*, whereas others found them to be low in type 1 and 2 diabetic patients *(130–132)*. Furthermore, some considered type 2 diabetes mellitus to be a relative hypogonadism state *(68,133)*.

When interpreting the results of total testosterone levels in diabetic patients, one has to take into consideration the sex-hormone-binding globulin (SHBG) levels, which has been found to be low in type 2 diabetic men *(68,69,132,133)*. The SHBG levels correlate positively with the improvement in the level of glycemic control and negatively with the degree of insulin-resistance *(133,134)*. Decreased production of SHBG might be explained by the negative effect of insulin on production of SHBG in the liver *(135)* and by the hyperinsulinemia seen in insulin-resistant states. It is important to note that SHBG levels are also lower in obesity, which is a common finding in type 2 diabetic patients.

When total testosterone and SHBG levels were measured together in type 2 diabetic men, it was found that their ratio was not changed and that free-testosterone level was normal *(68)*. Similarly, mean testosterone levels in type 1 and type 2 diabetic men complaining of impotence do not demonstrate a significant abnormality *(136,137)*. Thus, it is not clear to what extent changes in testosterone metabolism contribute to the impotence seen in diabetic patients.

The inconsistency in the reports on the effects of diabetes upon the hypothalamic–pituitary–gonadal axis in men might be explained, in part, by a lack of addressing potential confounding factors, such as the type of diabetes, level of obesity, level of glycemic control, age, time of sampling, and the methodology used in the measurement of the hormones.

Hypothalamic–Pituitary–Gonadal Axis in the Female

Although estrogens enhance insulin sensitivity in women *(138)*, the prevalence of type 2 diabetes is higher in women *(139)*. This may be related, in part, to the higher prevalence of female obesity *(140)*.

Lutenizing hormone (LH) and follicle-stimulating hormone (FSH) levels in postmenopausal type 1 diabetic women reveal a physiologic increase (146), whereas in type 2 diabetic women, this increase is blunted (141).

In women with type 2 diabetes, free-testosterone levels are increased *(68,69)*. In contrast, in men with type 2 diabetes, free-testosterone levels are normal, as has been addressed earlier. It is unclear what mechanisms lead to the hyperan-

drogenemia in type 2 diabetic women. Because the adrenal androgens are normal or only mildly increased in women with type 2 diabetes *(66,67)*, the androgen excess is probably mainly of ovarian origin. In premenopausal and postmenopausal type 2 diabetic women, bioavailable testosterone levels correlate positively with the glucose and insulin levels *(68,69,131,142)*. High serum insulin concentration may stimulate the activity of the ovarian steroidogenic enzymes *(143,144)*. This may also explain the increase in estrogen levels seen in type 1 and 2 diabetic women *(69,131,145–147)*.

In contrast to men, SHBG levels are elevated in type 1 premenopausal diabetic women *(145)*. On the other hand, SHBG levels are normal in insulin-treated postmenopausal type 2 diabetic women *(69)*. Finally, the total testosterone/SHBG ratio is increased in type 2 diabetic women *(68)*.

In regularly menstruating type 1 diabetic women, estradiol levels are elevated *(145)*. Similarly, in women with type 2 diabetes, total and bioavailable estradiol levels are increased *(69,131,146,147)*, and the estradiol levels correlate with the fasting plasma glucose levels *(131)*. In postmenopausal type 2 diabetic women, estrone (the main postmenopausal estrogen) is also increased *(68)*.

Because estrogens may have a protective effect on the heart in premenopausal women, one might wonder why premenopausal diabetic women who have higher levels of estrogen lose the sex-mediated protection against coronary heart disease. This phenomenon can be explained, in part, by the failure of the estrogens to stimulate basal nitric oxide (NO) release *(148)* as well as by an impaired NO biological activity in diabetes *(149)*.

Animal and human studies reveal that diabetes mellitus also affects progesterone metabolism and LH response to ovariectomy *(134,150)*. Progesterone levels are lower during the luteal phase in diabetic rats *(151)*, and insulin therapy partially corrects this abnormality *(152)*. In type 1 diabetic women, progesterone levels are decreased during the follicular phase but not during the luteal phase *(150)*. In addition, cultured granulosa cells derived from diabetic patients reveal decreased progesterone production *(153)*.

Taken together, it seems that type 2 diabetic women have a higher incidence of hyperandrogenemia and hyperestrogenemia. The latter may contribute to the increased risk of uterine cancer seen in these women *(154)*. The low progesterone and high androgen levels may contribute to the increased incidence of infertility seen in diabetes, which might improve with insulin therapy *(155)*.

Oxytocin

Lactation is divided into two phases: milk synthesis and milk release. Oxytocin is essential for the second phase. However, other hormones are also required for optimal lactation, including prolactin, cortisol, estrogen, progesterone, and insulin *(156)*.

In postpartum diabetic rats, both milk synthesis and milk release are decreased. These abnormalities are reversed by insulin therapy *(156,157)*. Labeling of oxytocin in the hypothalamus is increased in diabetic rats, indicating an increase in the synthesis of the hormone *(157–159)*. Increased oxytocin production was also shown in type 1 diabetic patients in the absence of osmolality changes *(160)*.

Differing from observations in the hypothalamus, immunoreactive levels of oxytocin in the posterior pituitary of diabetic rats are decreased, and insulin treatment reverses this defect *(157)*. These data may indicate increased hypothalamic synthesis as well as rapid pituitary release in diabetes.

Oxytocin is potentially involved in glucose homeostasis by increasing glycogenolysis *(158)* as well as gluconeogenesis *(161)*. Thus, in addition to the action of oxytocin on myoepithelial cells and the uterine myometrium, oxytocin may have a potential counter-regulatory effect by stimulating glucagon and possibly epinephrine in response to hypoglycemic episodes in type 1 diabetes *(162)*. This response to hypoglycemia is exaggerated in type 1 diabetic patients *(160)*.

Prolactin

Prolactin has an essential role in milk synthesis. Induction of diabetes in postpartum rats results in a reduction in serum prolactin level as well as in milk synthesis *(156,163)*. Also, prolactin response to suckling is decreased in diabetic rats *(163)*. Interestingly, although insulin treatment does not normalize serum prolactin levels in the diabetic rats, their milk production is completely regained *(163)*.

In spite of the unchanged circulating prolactin levels in nonpregnant diabetic animals, prolactin responses to different stimuli such as stress and TRH are decreased *(164)*.

Human studies reveal that in type 1 and type 2 diabetic men, prolactin levels are normal *(165,166)* or increased *(167, 168),* whereas levels in type 1 diabetic women are decreased *(169,170)*.

An abnormal and diminished circadian pattern of plasma prolactin is found in poorly controlled type 1 diabetic patients *(171,172)*, which may suggest hypothalamic dysfunction *(172,173)* or diminished pituitary responses to TRH *(174)*. The abnormality in prolactin production in diabetic patients may be related to the decreased insulin-mediated prolactin gene expression *(175)*.

There is no difference in the mean serum prolactin levels between type 1 and type 2 diabetics *(167,168)*, and no correlation was found between serum prolactin levels and the duration of diabetes, or the glycosylated hemoglobin levels *(168)*.

Taken together, it is unclear whether diabetes mellitus has a clinically significant effect on prolactin function. It is unlikely that changes in prolactin levels in diabetes mellitus lead to impotence. Also, prolactin levels in diabetic men of both types do not correlate with sexual potency *(167,168)*.

Vasopressin

Vasopressin is synthesized in the hypothalamus and released into the blood by the neurohypophysis in response to hyperosmolarity, hypovolemia, and stress *(176)*.

Plasma vasopressin levels are elevated in animal diabetes and in poorly controlled type 1 diabetic patients *(177–179)*, probably secondary to the hyperglycemia-related hypovolemia.

Although the basal discharge rate of vasopressinergic neurons is increased in diabetic rats *(180)*, the response to osmotic stimulation is relatively low. This blunted vasopressin response may reflect an osmoregulation dysfunction and may explain the lack of circadian vasopressin secretion seen in rats with uncontrolled diabetes mellitus *(181)*.

The sensitivity of vasopressin release in response to osmotic stimuli depends on the duration of the hyperglycemic state. A reduction in the sensitivity is noted in newly diagnosed untreated hyperglycemic patients *(182)*, whereas rapid insulin withdrawal in type 1 diabetes results in an unchanged or an increased osmoreceptor sensitivity during the hyperglycemic state *(183,184)*. However, other factors, such as sodium levels, volume status, effects of nonosmotic stimuli, and the integrity of the autonomic nervous system, have to be taken into account when interpreting these results.

Vasopressin storage in the pituitary's posterior lobe in patients with uncontrolled type 2 diabetes is reduced or depleted *(185–187)*. This is partially reversed with improvement in the glycemic control *(185)*.

Vasopressin receptors are classified as V1 and V2. The antidiuretic effect of vasopressin is mediated by V2 receptors, located at the collecting duct in the kidney. V1 receptors, present in the kidney, brain, and blood vessels, mediate vasopressin action on the vascular tissue and on hepatic glycogenolysis. In hyperglycemic states, vasopressin levels are elevated and the renal V1 receptors are downregulated *(188)*. This is not seen with either the antidiuretic V2 receptor or with its second-messenger system activity *(189)*.

Vasopressin may contribute to the diabetic complications. It may be involved in the early phase of diabetic nephropathy *(190)*. It has been demonstrated that urinary levels of aquaporin 2, the vasopressin-sensitive water channels that promote tubular water reabsorption, are lower in type 2 diabetic patients compared with control. This defect is reversed with improvement in the diabetes control *(191)*. Thus, the polyuria seen in the hyperglycemic state may be related, in part, to a decrease in the ability to concentrate urine because of this acquired form of relative nephrogenic diabetes insipidus. However, glycosuria secondery to increased glucose load remains the main reason for the polyuria seen in hyperglycemic states *(192)*.

Thyroid

Plasma thyroid hormones levels are generally normal in stable, controlled diabetic patients, and hormones levels are similar in individuals with type 1 or type 2 diabetes *(193)*. However, diabetes may also alter the hypothalamic–pituitary–thyroid peripheral axis at different levels.

At the periphery, uncontrolled diabetes mellitus, like many other nonthyroidal illnesses, causes a decrease in T3 and an increase in reverse T3 (rT3) levels *(194–196)*, reflecting an impairment in T4 peripheral monodeiodination *(197)*. There is a negative correlation between the T3 and glycosylated hemoglobin levels *(193)* and the most severe decline in T3 levels is seen in patients with diabetic ketoacidosis *(194–198)*. The abnormalities in thyroid hormone levels usually normalize after achieving better glycemic control *(194,199)*.

In addition to the disturbances in the peripheral metabolism of the thyroid hormones, experimental diabetes is associated with a primary impairment in hormone secretion and a diminished thyroidal response to thyroid-stimulating hormone (TSH) *(200)*.

The effect of diabetes on the hypothalamic–pituitary axis has been extensively studied. In diabetic rats, both a decrease in systemic TRH levels and in the hypothalamic TRH content along with a decreased serum TSH concentration were observed *(201,202)*, suggesting impairment at the hypothalamic level. In turn, the reduction in the hypothalamic secretion of TRH could contribute to the reduced plasma TSH and thyroid hormone levels *(203)*. However, diabetes in the rats may alter pituitary function independent of a hypothalamic effect *(204)*.

Evaluation of TSH secretion in type 1 and 2 diabetic patients reveals conflicting findings. TSH levels have been reported to be increased *(205,206)*, normal *(207–210)*, or decreased *(199)*. Similar conflicting results were found regarding the TSH response to TRH stimulation in diabetic patients *(198, 199,210,211)*, but the metabolism of exogenous TSH is not affected by diabetes *(208)*.

Nocturnal TSH peak, a sensitive marker of the central control of the hypothalamic–pituitary–thyroid axis, was found to be blunted in diabetes in both types *(212)*. These abnormalities in TSH secretion are reversed by better glycemic control *(197,212)*.

Consequently, in animal diabetes and in humans with uncontrolled diabetes, severe hyperglycemia may cause thyroidal abnormalities resembling secondary or tertiary hypothyroidism *(202,212)*.

Parathyroid Hormone and Calcium/Vitamin D Metabolism

Vitamin D_3 (Vit D) synthesized in the skin is processed in the liver to 25-hydroxyvitamin D_3 [25(OH) Vit D] and then in the kidney to the active metabolite 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2$ Vit D]. The main function of the Vit D system is to maintain constant plasma calcium (Ca) levels by increasing Ca absorption from the gut. Reports regarding plasma Ca levels vary in type 1 and type 2 diabetes. Low plasma-ionized Ca levels were reported in type 1 diabetic

patients *(213,214)*, whereas normal or increased serum Ca in type 1 and 2 diabetic patients have been described *(215–217)*.

Hypercalciuria is seen in animal and human diabetes *(218–220)*. Several factors may contribute to the increased urinary Ca, including intestinal hyperabsorption associated with intestinal mucosa hypertrophy, hyperfiltration, and osmotic diuresis *(221)*, and tubular defects *(222)*. The hypercalciuria tends to be more severe in type 1 than in type 2 diabetes *(218)*.

Rats with short-term insulin-deficient diabetes have impaired intestinal absorption of Ca *(223)*, probably secondary to low $1,25(OH)_2$ Vit D. Insulin is required for PTH stimulation of $1,25(OH)_2$ Vit D production *(224)*. However, rats with chronic diabetes show increased intestinal Ca absorption *(225)*, possibly secondary to intestinal mucosal hypertrophy and a compensatory increase in intestinal $1,25(OH)_2$ Vit D receptors *(226)*.

Reports concerning Vit D metabolism in both animal and human diabetes are inconsistent. 25(OH) Vit D and $1,25(OH)_2$ Vit D levels were reported to be low *(213,227–230)* or normal *(231–233)*. The decrease in $1,25(OH)_2$ Vit D levels may be secondary to a decrease in 1-α hydroxylation *(231)* or to a decrease in the binding protein *(223)*. The clearance of $1,25(OH)_2$ Vit D is not altered in animal diabetes *(224)*. Insulin therapy reverses the defect in $1,25(OH)_2$ Vit D production *(234,235)*.

The levels of calcitonin, which may have a stimulatory effect on the 1-alpha hydroxylase activity in the renal proximal tubule *(236)*, are decreased in animal diabetes and can be increased by insulin treatment *(220,237,238)*. However, in type 1 pediatric diabetics, a state of chronic C-cell stimulation and a reduction in calcitonin reserve has been observed *(239)*, which may play a role in the development of diabetic osteopenia. In type 2 diabetes, the calcitonin level seems to be normal *(240)*.

Inconsistent results were also reported with regard to $24,25(OH)_2$ Vit D levels and 24-hydroxylase activity in animal and human diabetes *(220,229,241,242)*. Infusion of glucose into normal rats reduces the activity of the 24-hydroxylase-enzyme *(242)*, which may account for the decrease in $24,25(OH)_2$ Vit D levels. Decreased receptors in the kidney may contribute to the decreased effect of $24,25(OH)_2$ Vit D in diabetes *(243)*.

The effects of diabetes on PTH levels vary and may depend on its duration. Short-term diabetes in rats increases PTH levels *(237)*, whereas rats with chronic diabetes have decreased PTH levels *(225,226)*. Others found normal PTH levels but a decreased responsiveness to PTH in converting 25(OH) Vit D to $1,25(OH)_2$ Vit D *(220,241)*. Reports concerning PTH levels in diabetic patients vary. Some investigators found that PTH levels in type 1 and type 2 diabetics remain in the normal range *(244–246)*, whereas others reported decreased PTH levels in patients with type 1 diabetes *(218)*. However, these levels may be inappropriate to the ambient plasma Ca levels in the diabetic patients *(215–217)*. PTH levels in patients with type 1 diabetes are lower than levels seen in type 2 diabetes *(218)*. Although PTH may increase insulin production *(247)*, it may decrease the hormone's peripheral action *(248)*.

Interestingly, there is a clear link between the prevalence of diabetes mellitus and primary hyperparathyroidism. The prevalence of diabetes mellitus in primary hyperparathyroidism is around 8%, and that of primary hyperparathyroidism in type 1 and 2 diabetic patients is around 1%. Both values are about threefold to fourfold higher than the expected prevalence in the general population *(249)*. The increased incidence of insulin resistance in primary hyperparathyroidism *(250)* may explain the higher prevalence of diabetes *(251)* in these patients. On the other hand, the increased incidence of primary hyperparathyroidism in diabetic patients *(252)* may be attributed to the chronic stimulation of the parathyroid glands as a result of low $1,25(OH)_2$ Vit D *(238)*.

Patients with type 1 diabetes have an increased incidence of osteopenia and bone fractures *(232,253,254)*. The low-turnover osteopenia seen in type 1 diabetes is severer in those with microalbuminuria *(217)*. The etiology of the osteopenia is multifactorial and may involve low Ca and low $1,25(OH)_2$ Vit D levels, hypercalciuria, and impaired osteoid formation *(255)*. Less consistent are the observations in patients with type 2 diabetes *(253,256,257)*.

The Adipose Endocrine System

Recently, it has been recognized that the adipose tissue is not only a fat reservoir but also a source for several metabolic factors and hormones such as leptin, adiponectin, resistin, rennin–angiotensin components, TNF-α, and plasminogen activator inhibitor-1 (PAI-1).

Leptin

Leptin circulates in the blood at levels proportionate to the body fat mass and acts in the brain to reduce food intake and stimulate energy expenditure *(258, 259)*.

It has been shown in both animals *(260)* and less clearly in humans *(261,262)* that the expression of leptin mRNA may be modulated by insulin. Although not universally accepted *(263,264)*, some studies found a positive correlation between plasma leptin and plasma insulin levels *(263,265,266)*.

Interestingly, the elevated plasma leptin levels in hyperinsulinemic individuals were found to be independent of the presence of obesity *(263,267)*. Data are inconsistent concerning the acute effects of hyperinsulinemia on leptin production *(264,268,269)*, and chronic hyperinsulinemia might be needed *(262,270)*. In STZ-induced diabetes in pigs, leptin mRNA levels are decreased *(271)*, and insulin treatment raises the leptin mRNA levels in the adipose tissue to levels seen in controls *(271)*.

It was suggested that glucose uptake in the fat cells, and not a direct effect of insulin, regulates leptin secretion *(272)*. Some investigators found a positive correlation between

plasma leptin and plasma glucose *(273)*, whereas others did not *(274)*. A negative correlation between glycosylated hemoglobin and serum leptin levels was described in type 2 diabetes *(275)*. However, plasma leptin levels in diabetic animals and in type 2 diabetic humans are similar to those of their controls when adjusted for body mass index (BMI) *(258,276)*.

In nondiabetics, postprandial leptin levels do not change *(277)*. In contrast, diabetic patients on insulin therapy show an increase in plasma leptin levels postprandially *(268,269)*. However, in patients with type 2 diabetes who are not on insulin therapy, there are no acute changes in circulating leptin levels postprandially despite an increase in postprandial insulin and glucose *(274)*.

In type 1 diabetic patients treated with insulin, the serum leptin level is increased *(278)*. However, the increased leptin levels in the insulin treated type 1 diabetics is probably a result of changes in BMI *(278,279)* and not the result of a direct effect of insulin *(280)*.

It has been suggested that leptin may have a physiological and clinical role in pancreatic beta-cell function and insulin secretion. Leptin may inhibit glucose-stimulated insulin secretion and insulin gene expression in animal and human cultured cells *(281,282)*.

It has been proposed that leptin may play a role in the pathophysiology of diabetic retinopathy. In fact, leptin levels are elevated in patients with diabetic retinopathy even after adjusting for BMI *(283,284)*. Additionally, leptin levels are reported to be increased in the vitreous of patients with diabetes *(284),* and these levels correlate with the severity of the diabetic retinopathy *(284)*.

Observations that leptin may increase glucose uptake and type I collagen in mesangial cells and stimulate the intraglomerular TGF-β system *(285)* in kidneys of diabetic animals could suggest that leptin may also be involved in the glomerulosclerotic process of diabetic nephropathy. Elevated serum leptin levels are found in patients with diabetic nephropathy and renal failure, but these elevated levels may reflect decreased leptin clearance *(286)*.

Adiponectin

Adiponectin is a recently discovered adipocyte-derived factor *(287)*. Adiponectin may have anti-inflammatory *(288)* as well as antiatherogenic effects *(288,289)*.

The reduced adipose tissue apM1 gene expression in ob/ob mice *(290)* and in obese Caucasians with type 2 diabetes *(291)* has led to the hypothesis that adiponectin may have a role in the pathogenesis of obesity and type 2 diabetes *(291)*.

Adiponectin levels are decreased in obesity *(292)*, type 2 diabetic monkeys *(293)*, type 2 diabetic humans *(294)*, and other insulin resistant states *(295)*, irrespective of the ethnicity of the individual *(296)*. The hormone's levels may be related to the level of insulin sensitivity *(296,297)*, and weight reduction may increase serum leptin levels *(298)*.

Replacement treatment with recombinant adiponectin in physiological doses improve insulin sensitivity and ameliorates the hyperglycemia *(295)*. Interestingly, plasma adiponectin levels are lower in diabetics with coronary artery disease (CAD) as compared with those in diabetics without CAD *(294–296)*. Thus, the low level of adiponectin in type 2 diabetics may contribute to the increased risk of atherosclerotic disease in this condition.

The antidiabetic property of adiponectin may be secondary to an increased influx and combustion of free fatty acids in the skeletal muscle, thereby reducing its triglyceride content *(295)*. Adiponectin may also enhance insulin action and suppress hepatic glucose production *(298)*. The role of adiponectin in the pathogenesis of diabetes needs further investigations.

Resistin

Resistin is a signaling molecule that gets induced during adipogenesis. Resistin levels are increased in animals with diet-induced and genetic obesity that display insulin resistance. The insulin-antagonistic effect of resistin, which has been shown in vitro and in vivo *(299),* may be mediated by suppressing the insulin stimulation of glucose uptake. Therefore, it has been initially proposed that resistin could potentially be a link between obesity and diabetes *(299)*.

The role of resistin in human diabetes is less clear. In fact, recent human studies did not detect significant correlation between diabetes and resistin *(300–303)*. Similar negative findings have been found concerning the relationship of resistin to obesity and insulin-resistance states *(304)*. The discrepancy between the significance of the role of resistin in animals and in humans may be explained, in part, by the fact that human fat cells, in contrast to rodent fat cells, do not express resistin at all or only at extremely low levels in some individuals *(301)*. Therefore, resistin may not be the hormonal link between obesity and human diabetes, as was thought earlier *(302)*.

Plasminogen Activator Inhibitor-1

Plasminogen activator inhibitor-1 (PAI-1) is a biochemical marker of impaired fibrinolysis. High PAI-1 levels have been found in insulin-resistant states such as hypertriglyceredemia *(305)*, obesity *(306),* CAD *(307),* and type 2 diabetes *(308)*. Levels are also increased in diabetic rats *(309)*.

In type 2 diabetes, a positive correlation is found between PAI-1 levels and the insulin and insulin resistance levels *(310–312)*. Interestingly, although insulin stimulates hepatic synthesis of PAI-1 *(313),* insulin infusion reduces PAI-1 levels *(314,315)*.

The PAI-1 activity is increased in type 2 diabetes independent of insulin and triglyceride levels *(316)*. This may suggest a direct stimulatory effect by the increased glucose levels. The PAI-1 levels have been reported to be elevated also in the atherosclerotic lesions of diabetic patients *(317)* and in the aortic wall in animal diabetes. Also, PAI-1 levels may also be elevated in type 1 diabetes mellitus *(318),* but this was not confirmed *(319)*.

Table 1
Summary of the Observed Hormonal Changes in Type 1 and Type 2 Diabetic Patients

Hormone	Changes in type 1 diabetes (ref.)	Changes in type 2 diabetes (ref.)
Growth hormone	Increased *(6,7)* Pulsatile changes *(8,21)*	Pulsatile changes *(22)*
IGF-1	Decreased *(6,7)*	Decreased *(28)*
ACTH	—	Increased *(46–48)* Pulsatile changes *(49,50)*
Cortisol	Increased *(57)*	Increased *(48)*
DHEA-S	Normal *(67)*	Decreased *(60–63)*
Serum RAS	Normal *(77)* Suppressed *(77,82)*	Normal *(77)* Suppressed *(76–78)*
Intrarenal RAS	Strong evidence of being activated *(75–77)*	Strong evidence of being activated *(75–77)*
LH, FSH in males	Normal *(125)* Increased *(126)*	Normal *(125)* Increased *(127)*
LH, FSH in females	Normal *(146)*	Low in postmenopausal *(141)*
Free testosterone in males	Normal *(129,130)* Decreased *(131)*	Normal *(125)* Decreased *(68,127,131,132)*
Free testosterone in females	Increased *(145)* Normal *(146)*	Increased *(68,69,131)*
Estrogen in females	Increased *(146)* Decreased *(142)*	Increased *(69,131)*
Progesterone	Decreased in follicular phase *(150)* Normal in luteal phase *(150)*	—
Prolactin in females	Decreased *(169,170)*	—
Prolactin in males	Normal *(165,166)* Increased *(167,168)*	Normal *(165,166)* Increased *(167,168)*
Vasopressin	Increased in poorly controlled *(177)*	Increased in poorly controlled *(178)*
TSH	Normal *(207,210)* Blunted nocturnal peak *(212)*	Normal *(207,210)* Blunted nocturnal peak *(212)*
Free thyroxin	Normal *(193)*	Normal *(193)*
Calcitonin	Chronic C-cell stimulation *(239)*	Normal *(239)*
Parathyroid hormone	Normal *(244,245)* Decreased *(218)*	Low-normal to normal *(235)*
Leptin	Normal *(279)* Decreased in untreated *(278)* Increased in treated *(278)*	Normal *(274,276)* Increased in diabetic nephropathy *(286)*
Adiponectin	—	Decreased *(291,294)*
PAI-1	Increased *(318)*	Increased *(308)*

Abbreviations: IGF-1: insulinlike growth factor-1; ACTH: adrenocorticotropic hormone; DHEA-S: dehydroepiandrosterone sulfate; RAS: renin–angiotensin system; LH: luteinizing hormone; FSH: follicle-stimulating hormone; TSH: thyroid-stimulating hormone; PAI-1: plasminogen activator inhibitor-1.

In summary, PAI-1 may be considered to be one of the features of the insulin-resistance syndrome that may contribute to the increased incidence of CAD in diabetic patients *(302)*. Thus, reducing the PAI-1 level by targeting hyperinsulinemia and correcting the hyperglycemia, in the treatment of diabetic patients, may have a protective effect against potential cardiovascular and thrombotic events.

Summary

It is clear from this review that the entire endocrine system is not functioning normally in individuals affected by diabetes mellitus. Both the hormone secretion and action may be affected.

Tables 1 and 2 summarize the major findings in the hormonal status in patients with type 1 and type 2 diabetes and in animal diabetes. More details are given in the text in the subsection for each hormone.

The striking feature is the heterogeneity in the findings. This heterogeneity may reflect the heterogeneity of the diabetes syndrome, in which there is a continuous dynamic interplay between a continuous decrease in insulin secretion and a more constant level of increased insulin resistance.

The level of the metabolic control may also play a significant role in determining the degree of impairment in the hormone's function. However, as detailed in the text, not all of the observed abnormalities in the hormones' function

Table 2
Summary of the Observed Hormonal Changes in Diabetic Animals

Hormone	Changes in animal diabetes (ref.)
Growth hormone	Decreased *(3,4)*; pulsatile changes *(5)*
Epinephrine	Increased *(96)*
Serum RAS	Suppressed *(78)*
Intrarenal RAS	Activated *(77,78)*
LH, FSH in males	Decreased or normal *(118–122)*
LH, FSH in females	Relatively low *(134,150)*
Testosterone in males	Decrease *(118,119)*
Progesterone	Decreased in luteal phase *(151)*
Prolactin in pregnant	Normal with blunted response to stimuli *(164)*
Prolactin in postpartum	Decreased with decreased milk synthesis *(156,163)*
Vasopressin	Increased with blunted response to stimuli *(180)*
TRH, TSH	Decreased *(201–203)*
Calcitonin	Decreased *(237)*
Parathyroid hormone	Increased in short-term diabetes *(237)*; decreased in long-term diabetes *(225,226)*
Leptin	Normal *(258)*
Resistin	Increased (299)
Adiponectin	Decreased *(293)*
PAI-1	Increased *(309)*

Abbreviations: RAS: renin–angiotensin system; LH: luteinizing hormone; FSH: follicle-stimulating hormone; TRH: thyrotropin-releasing hormone; TSH: thyroid-stimulating hormone; PAI-1: plasminogen activator inhibitor-1.

are fully reversed by an improvement in the metabolic control or by insulin treatment. This lack of full reversibility may result from the following:

1. The metabolic condition is not fully normalized.
2. The length of improvement in the metabolic control was not sufficient to fully reverse the abnormalities in the hormone's function.
3. Some of the changes in the hormone's function become irreversible.

However, it is also potentially possible that the observed abnormalities in the hormones' function in diabetes may partially stem from more basic defects at the cellular level. Such defects may include the impairments in cellular calcium homeostasis *(320)* that was reviewed earlier.

It is not clear to what extent these additional changes in the hormonal milieu contribute to the observed complications seen in diabetes. For example, changes in androgens status and catecholamine function may be of significance in the pathogenesis of the cardiovascular complications seen in diabetes.

However, it is clear that more investigations are needed. These should include the following:

1. Studies that will explore the mechanisms leading to the changes in the hormone's function in diabetes.
2. Studies that will explore the role of the changes in the hormonal milieu in the pathogenesis of the diabetes syndrome.
3. Studies that will explore the role of the abnormalities in the hormonal milieu on the diabetic vascular complication.

Such investigations may contribute to our better understanding of the diabetes condition.

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