

## **The gender-specific approach to diabetes: what is known and what is yet to learn**

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Gender-specific care of diabetic patients is poorly developed, with few applications in the daily practice of endocrinologists and diabetologists. The large, prospective trials made in the past 20 years have assumed that results related to efficiency of glucose-lowering therapies as well as management of hyperglycaemic-related complications could be applied without distinction to men and women. Whereas a much higher number of men than women were included in these trials, no gender-specific analysis of the results was made. Actually, beyond obvious gynecologic considerations (gestational diabetes mellitus and pre-conception care), which concern diabetic women solely, the *Standards of Medical Care in Diabetes Mellitus* annually published by the American Diabetes Association gives little or no consideration to gender-specific recommendations. However there are significant differences between diabetic women and men that can be found in the medical literature. In this presentation, I will review and discuss the most relevant topics: some known risk factors for developing diabetes mellitus differ between men and women; different sensitivity of screening and diagnostic tests (fasting glucose, oral glucose tolerance test) for diabetes mellitus in men and women; all cardiovascular risk factors (hypertension, hyperlipidemia, obesity, inflammation) in diabetic women have worst effects on mortality and morbidity than in diabetic men; some medications, such as thiazolidinediones, do not have the same safety profile in diabetic women and men (significantly more fractures in the former than in the later) whereas another drug such as aspirin has a different gender-efficacy profile in primary cardiovascular prevention.

These observations could be regarded as trivial, were it not for a distressing clinical endpoint observed in a recent meta-analysis: diabetic men benefitted from a significant improvement in total cardiovascular and all-cause mortality in the last 30 years, whereas diabetic women had no improvement at all. So what is wrong in the standard management of diabetic women which can explain such inequality? Answering this question is challenging. For example, data suggest differences in pathophysiology of insulin resistance and endothelial dysfunction between men and women, thus partly explaining increased cardiovascular morbidity mortality. Furthermore, it appears that women are usually less aggressively treated than men. The combination of both factors may be particularly deleterious to diabetic women.

The concept of *gender-medicine* is gaining in popularity and influence in many fields, but is only at its infancy in regard to management of diabetes mellitus. The first lesson we have to learn is that women should be treated at least as well as men, and reach the same therapeutic targets. Only then we may identify the critical factors that need to be addressed to improve gender-specific care of patients with diabetes mellitus, and maybe change the therapeutic goals for women.

## One system, two genders: bone and gonadal steroids

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Mammalian bones cells express low concentrations of specific intracellular and membranal receptors for estrogens and androgens. Those cells also respond to the hormones by modulating different parameters. In our studies we demonstrated that: rat bone *in vivo* and rat bone cells *in vitro* responded sex-specifically to gonadal steroids in stimulation of both cell proliferation as measured by monitoring DNA synthesis and the specific activity of the BB isozyme of creatine kinase, a marker for hormonal responsiveness. Similar results were also demonstrated *in vivo* in mouse bone and in primary cultures of human osteoblast-like cells *in vitro* and in cell lines from both rat and human bone. In these systems female- derived bone responded only to estradiol-17 $\beta$  (E2) and male- derived bone cells responded only to dihydrotestosterone (DHT). The epiphyseal cartilage cells both *in vivo* and *in vitro*, on the other hand, responded to both E2 and DHT. The sex-specific response of bone cells to gonadal steroids was modified by manipulation of the endocrine environment in early development as was demonstrated in young rats or mice after gonadectomy, in pre-natally or neo-natally androgenized female rats and in androgen- receptor deficient (Tfm) male rats. Vitamin D and its non-hypercalcemic analogs up-regulated the sex-specific response of skeletal tissues both *in vivo* and *in vitro* from rat, mice and human. Bone marrow (BM) which contains committed osteo-progenitor cells, when transplanted into mice under the renal capsule formed after 21 days bone ossicles originated from the donor cells. The response of this new bone to E2 or DHT was according to the gender of the donor. On the other hand demineralized bone or tooth matrix (DTM) particles implanted under the skin induce bone formation by the pluripotent mesenchymal cells of the recipient, which responded to E2 and DHT according to the gender of the host. BM from femoral rat bone in culture was differentiated into bone cells which responded to the gonadal steroids sex- specifically according to the origin of the donor, with the loss of this specificity in bone cells originated from BM from gonadectomized rats. Human osteoblasts showed also sex-specific responsiveness not only to E2 but also to the estrogen mimetic anti-idiotypic antibody and to different native and synthetic phytoestrogens. The sex-specific response was also demonstrated in both human and rat bone cells by measuring membranal originated responses such as [Ca<sup>2+</sup>] mobilization. Of interest is the fact that male bone cells which did not respond to estrogenic compounds expressed estrogen receptors similar to female derived bone cells, suggesting post- receptor mechanism(s). It is also important to note that the "less differentiated" cells of the epiphyseal cartilage which can be considered as "pro-osteoblasts" and the "de-differentiated" bone cells derived from gonadectomized animals lost their sex-specific response to gonadal steroids. In conclusion cultured bone cells from different origins and mammals *in vivo* respond sex-specifically to gonadal-steroids by changes in both intracellular and membranal parameters, in a mechanism which is still not known. Whether this implies also for human bone *in vivo* is yet to be established.

## **From gender to transgender: sex hormones and the brain**

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The brain is a sexually dimorphic organ. Brain structure differences that result from the interaction between sex chromosome genes, gonadal hormones and developing brain cells are thought to be the basis of sex differences in a wide spectrum of behavioral and cognitive characteristics. Important insights on the hormonal effects on gender identity and sexual orientation have been obtained from patients with disorders of sexual development. Nevertheless, the degree of masculinization of the external genitalia may not reflect the degree of masculinization of the brain and its impact on gender identity. Finally, transsexual people have genital differentiation concordant with chromosomal sex, with normal circulating levels of sex hormone steroids, suggesting that other as yet unidentified mechanisms are involved in gender identity disorders.