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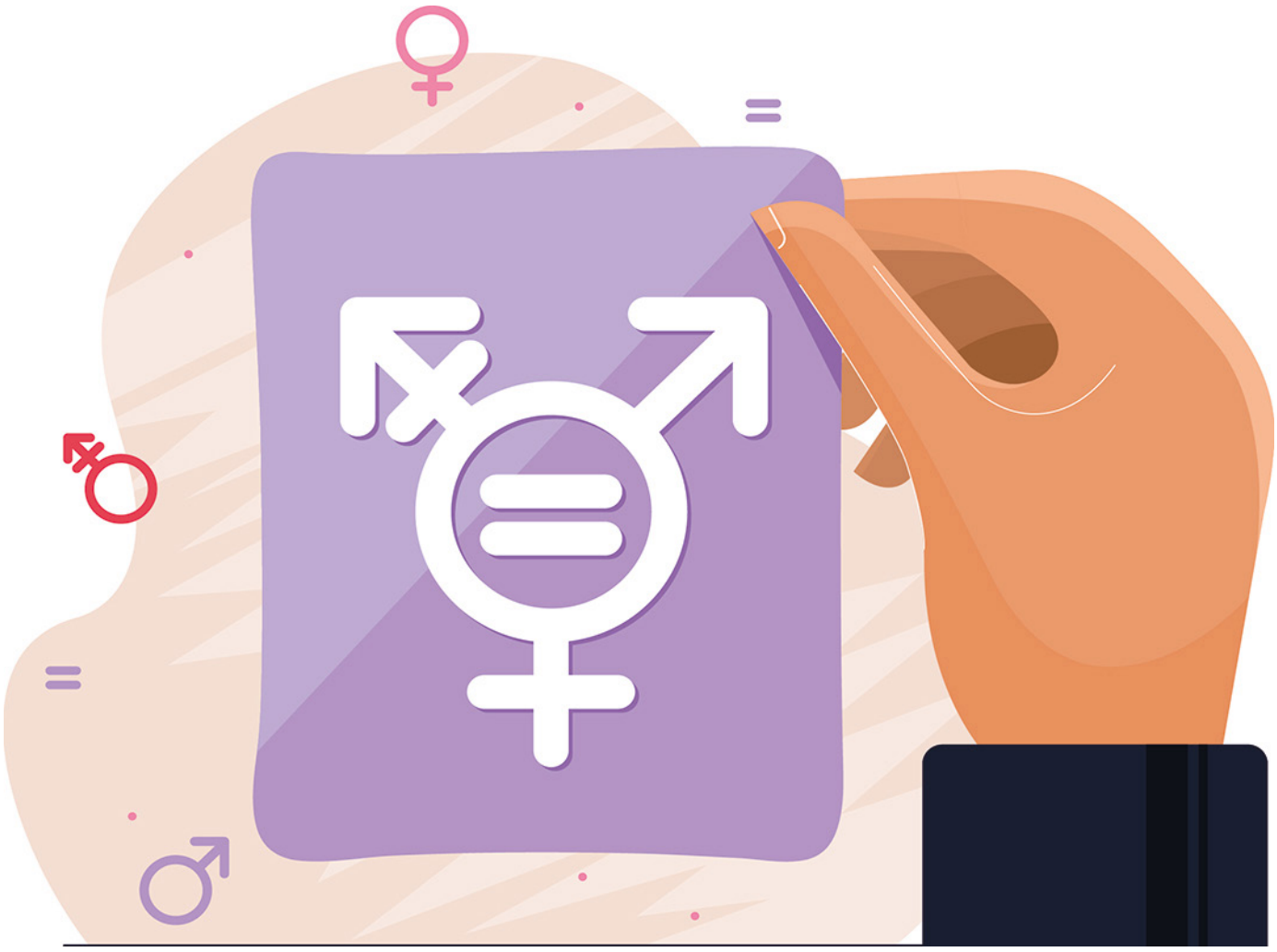

Type 1 diabetes mellitus and a gender perspective

Type 1 diabetes mellitus (T1DM) is a chronic metabolic disease characterized by autoimmunity against pancreatic beta cells, leading to absolute insulin deficiency. This lack of insulin prevents adequate glucose utilization by peripheral tissues, resulting in sustained hyperglycemia and disturbances in carbohydrate, lipid, and protein metabolism.

From a pathophysiological standpoint, T1DM arises from a complex interaction between genetic, immunological, and environmental factors. Genetic predisposition is strongly associated with certain alleles of the major histocompatibility complex (HLA), particularly the HLA-DR3, DR4, and DQ8 haplotypes, which confer an increased risk of developing pancreatic autoimmunity. However, genetics alone is not sufficient: environmental triggers are required, such as viral infections (enteroviruses, Coxsackie B, SARS-CoV-2), early exposure to dairy proteins, vitamin D deficiency, or alterations in the gut microbiota. Some studies have suggested that environmental triggers, including psychological stress, may initiate an autoimmune response against pancreatic β cells in genetically predisposed individuals.

It is well established that the incidence rate of T1DM has shown a sustained global increase, particularly in pediatric and adolescent populations. According to data from the International Diabetes Federation (IDF) and the Diabetes Atlas 2024, the estimated global incidence is close to 15–20 cases per 100,000 inhabitants per year, although with marked geographic variability.

T1DM AND SEX

T1DM shows several relevant differences according to sex, affecting incidence, clinical manifestations, immunological features, and complications.

Incidence and susceptibility

Type 1 diabetes mellitus exhibits an unequal distribution between men and women depending on geographic region and environmental context. In countries with a high incidence of T1DM, such as the Nordic or northern European countries, a predominance of male cases has been observed. In contrast, in regions with lower incidence, such as Mediterranean or Asian countries, the proportion tends to equalize or even be slightly higher in women.

This pattern suggests that environmental factors (viral infections, vitamin D exposure, latitude, diet) interact differently with genetic and immunological factors in each sex.

Differences in genetic susceptibility are also relevant: HLA alleles confer different levels of risk depending on sex, and certain genes located on the X chromosome may modulate immune responses, providing women with either greater resistance or, conversely, a more intense autoimmune response depending on the context.

Immunological factors

Women generally show a greater predisposition to autoimmune diseases, and T1DM is no exception. This tendency is explained by the influence of sex hormones on immune regulation and by the double dose of immunomodulatory genes on the X chromosome, which may escape inactivation and enhance immune system reactivity.

In clinical practice, this translates into a higher frequency of associated autoimmune diseases in women with T1DM, such as Hashimoto's thyroiditis, celiac disease, pernicious anemia, or autoimmune adrenal insufficiency. In addition, titers of autoantibodies against pancreatic antigens (anti-GAD65, anti-IA2, anti-ZnT8) tend to be higher and more persistent in women.

In contrast, men tend to exhibit a less exuberant immune response but with a more abrupt onset of pancreatic beta-cell destruction, which in some cases may translate into a more rapid progression toward insulin dependence.

Age at onset

Furthermore, differences have been described in the timing of disease onset. Some studies suggest a slightly earlier onset in females than in males, particularly during childhood or early adolescence. In males, T1DM more frequently appears during late adolescence or early adulthood.

These differences may be modulated by the hormonal changes of puberty, which influence insulin sensitivity and autoimmunity. In women, peaks of estrogen and progesterone may act as immunological triggers in genetically predisposed individuals. In addition, specific periods of vulnerability exist, such as the postpartum period, during which an increased risk of autoimmune onset has been observed due to immune reactivation following the phy- »

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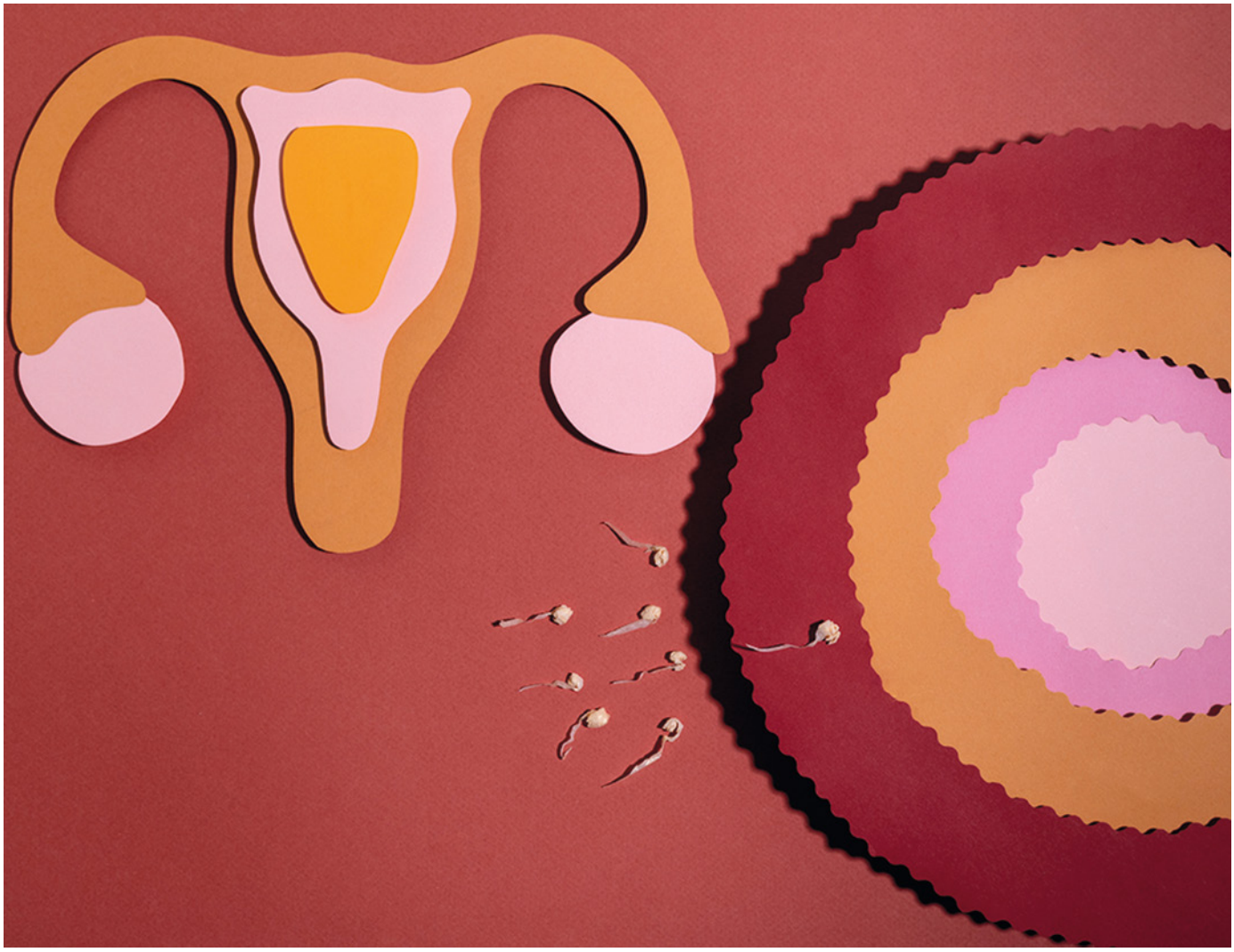


siological immunosuppression of pregnancy.

Metabolic control and complications

Sex also influences metabolic control and the evolution of chronic complications. Several studies have shown that women with T1DM generally present higher HbA1c levels than men, which may reflect differences in therapeutic adherence, disease perception, or physiological response to insulin.

Despite poorer average glycemic control, women tend to have lower body mass and less insulin resistance, although this advantage may be lost after menopause. Moreover, postmenopausal women with T1DM have a higher relative cardiovascular risk than men with T1DM, as the loss of estrogen's protective effect combines with dyslipidemia and hyperglycemia-induced chronic inflammation.

In men, metabolic control tends to be more stable, but with a greater tendency to develop insulin resistance and overweight in adulthood. They also more frequently present peripheral neuropathy and retinopathy.

On the other hand, women have a higher risk of diabetic ketoacidosis (DKA), especially at diagnosis or during periods of metabolic decompensation associated with hormonal and psychosocial factors, including pregnancy.

Reproductive aspects

T1DM has specific implications for reproductive function in both sexes.

In women, chronic hyperglycemia can alter the hypothalamic–pituitary–gonadal axis, leading to menstrual irregularities, delayed puberty, or dysmenorrhea. Poor glycemic control is associated with an increased risk of infertility and pregnancy complications, such as spontaneous abortion, fetal malformations, or preterm delivery. Pregnancy in women with T1DM requires close monitoring, as insulin requirements increase significantly (particularly in the second trimester), and metabolic control must be optimal to avoid maternal–fetal complications.

» In men, long-standing T1DM may cause erectile dysfunction, ejaculatory disorders, and impaired spermatogenesis, generally due to autonomic neuropathy and diabetic microangiopathy. Decreased testosterone levels have also been described in some patients, contributing to fatigue, loss of muscle mass, and reduced quality of life.

Conclusion

Although the disease can affect both sexes, there are clear differences in incidence, autoimmune signs, metabolic control, and complications.

T1DM AND TRANSGENDER PEOPLE

The term trans people encompasses individuals whose gender identity or expression differs from the sex assigned at birth.

Over the past 20 years, statistics have shown a notable increase in the prevalence of people who identify as transgender or who seek medical care related to gender transition.

In recent studies conducted in high-income countries, estimated prevalence ranges between 0.3% and 0.6% of the adult population, although figures vary widely depending on inclusion criteria. In younger populations, particularly adolescents, prevalence may exceed 1–2%, reflecting a substantial increase vs previous decades.

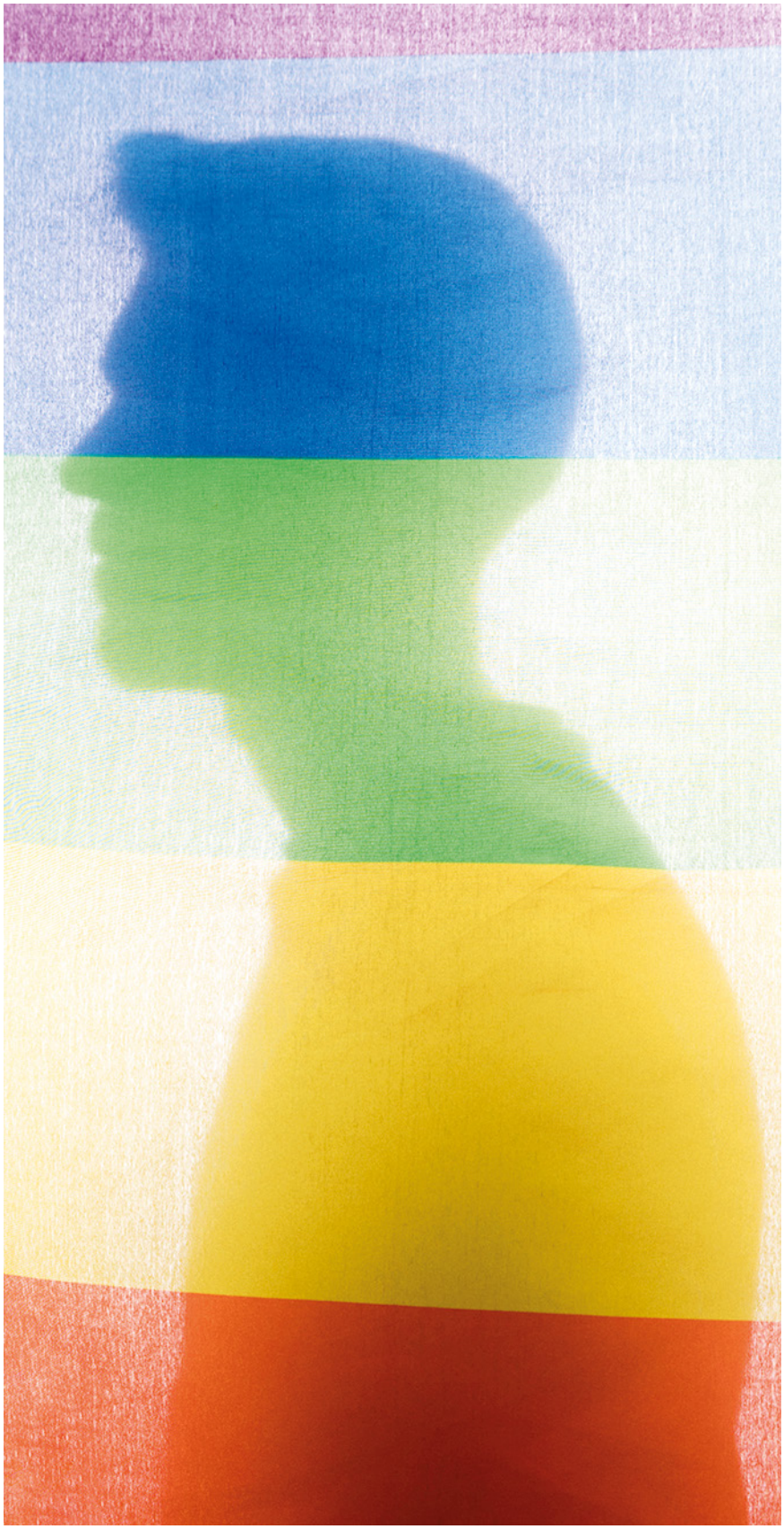
This increase is not interpreted as a "true" rise in the biological frequency of transgender identities, but rather as greater visibility and recognition due to several factors:

1. Greater social and legal acceptance, reducing fear of expressing gender identity.

2. Diagnostic reforms: changes in clinical manuals (DSM-5, ICD-11) removed the pathologizing concept of "gender identity disorder" and replaced it with a framework of "gender incongruence," centered on personal experience.

3. Expanded access to information and online communities, facilitating identification and peer support.

4. Improved access to specialized healthcare, with referral units for hormone therapy and psychological support. »



5. Increased awareness in education and mental health, promoting earlier diagnosis and stigma-free support.

The relationship between **T1DM** and transgender people is an emerging topic in the medical literature. **Although systematic studies** remain scarce, **clinical, metabolic, and psychosocial factors linking both realities are beginning to be identified**.

Clinical interest in the intersection between these groups lies in the fact that management of a chronic metabolic disease such as T1DM must be carefully adapted in individuals receiving estrogen or testosterone therapy, as these treatments influence insulin sensitivity, lipid profile, and cardiovascular risk.

Incidence rate and coexistence

Currently, there are no data indicating that transgender people have a higher incidence rate of T1DM compared with the cisgender population. However, it has been observed that within the transgender community, autoimmune diseases in general (such as autoimmune thyroiditis or lupus) may have a slightly higher frequency, suggesting possible shared immunological factors or increased diagnostic vigilance.

In endocrinology clinical registries, cases of transgender people with T1DM are rare, but their number has increased due to growing access to specialized healthcare and recognition of gender diversity in health databases.

Interactions with hormone therapy

The most relevant aspect of the relationship between T1DM and transgender people concerns the metabolic effects of gender-affirming hormone therapy (GAHT):

a) Transfeminine individuals (trans women, assigned male at birth)

Estrogen treatment (with or without an-

» tiandrogens) may cause a slight decrease in insulin sensitivity and an increase in peripheral insulin resistance, particularly with oral estrogens. This effect is milder than in type 2 diabetes, but in individuals with T1DM it may require adjustments in insulin dosing.

In addition, estrogens can modify lipid profiles and increase thrombotic risk, requiring careful monitoring of glycemia, lipids, and blood pressure. This effect may be mitigated by transdermal administration.

b) Transmasculine individuals (trans men, assigned female at birth)

Testosterone therapy tends to increase muscle mass and reduce body fat, often improving insulin sensitivity.

However, it may also increase hematocrit, alter lipid profiles, and induce a mild proinflammatory state.
In patients with T1DM, glycemic control usually improves or remains stable after initiating testosterone, although some report glycemic fluctuations during the early phases of treatment.

In both cases, close monitoring and coordinated care between general endocrinology, transgender endocrinology, and diabetes nursing are essential.

Psychosocial factors and therapeutic adherence

Transgender people with T1DM may face greater challenges in disease self-management due to emotional and social factors.

Gender dysphoria, anxiety, or depression associated with stigma may reduce adherence to insulin therapy or glycemic monitoring.

Conversely, initiation of the gender-affirmation process often improves psychological well-being, positively impacting diabetes self-management.

The presence of a multidisciplinary team sensitive to gender diversity improves quality of life and metabolic control in these patients.

Immunological perspective (hypotheses under study)

Some authors have proposed a possible interaction between sex hormones and autoimmunity, given that estrogens and androgens modulate immune responses.

- Estrogens tend to enhance autoimmune responses, whereas androgens attenuate them.
- This has led to the hypothesis that hormone therapy could theoretically modulate the risk or course of autoimmune diseases, including T1DM, although current evidence is insufficient to confirm this.

To date, no studies have demonstrated that gender-affirming hormone therapy either triggers or protects against T1DM. D

CONCLUSIONS

The relationship between type 1 diabetes and transgender people is based primarily on clinical and metabolic aspects rather than on increased autoimmune incidence rate. Transgender individuals with T1DM require personalized endocrinological management, as hormone therapies may modify insulin sensitivity and cardiovascular risk profiles.

In addition, psychosocial factors and access to healthcare are key determinants of glycemic control and treatment adherence. Integrating a gender perspective into diabetes care is essential to provide comprehensive, inclusive, and evidence-based healthcare.

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