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Advanced Technology (Continuous Glucose Monitoring and Advanced Hybrid Closed-Loop Systems) in Diabetes from the Perspective of Gender Differences

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Abstract: An ever-growing body of evidence suggests that sex and gender influence the pathophysiology, incidence, prevalence, clinical manifestations, course, and response to therapy of diabetes. Sex and gender differences are particularly evident in type 1 diabetes, especially in patients using advanced technologies (CGM and AHCL), as they are factors that interact with each other and have an impact on adherence to therapy, which affects not only metabolic compensation, but also, therefore, the prevention of complications and quality of life.

Keywords: type 1 diabetes; CGM; AHCL; gender medicine

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1. Introduction

Since the discovery of insulin, there has been a progressive evolution of diabetes treatment over the years, which has affected both the way of monitoring blood sugar and insulin delivery, revolutionising the management of insulin-dependent diabetes. The turning point came in 2000 with the introduction of continuous glucose monitoring (CGM) and the first miniaturised insulin pumps (CSII) equipped with advanced functions; from the integration of the two devices, it was possible to create the SAP (Sensor Augmented Pump) system; from this moment on, the development of technologies has undergone an acceleration, up to the creation and appearance on the market of the first artificial pancreas system (Automatic Insulin Delivery—AID), closed-loop, and hybrid systems (HCL—Hybrid Closed Loop) a century after the discovery of insulin (Figure 1) [1].

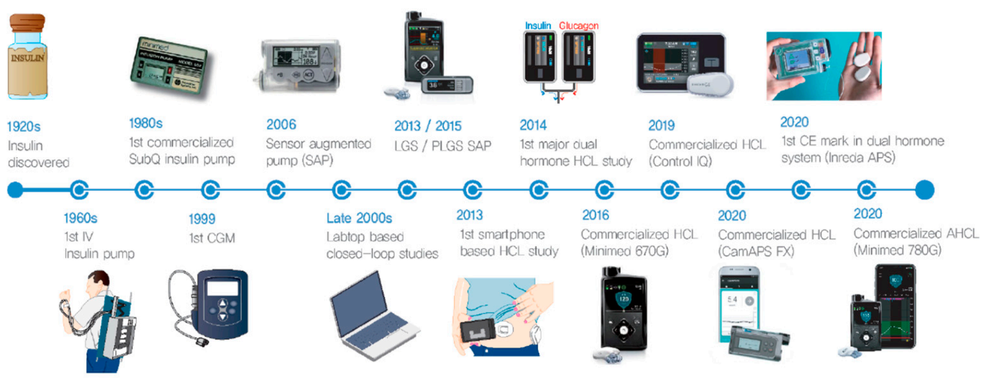

Figure 1. Technological evolution in diabetes therapy.

2. Closed-Loop Systems

The forerunner of closed-loop systems can be considered the SAP system, which, through its LGS (Low Glucose Suspend) and PLGS (Predictive Low Glucose Suspend) modes, allows the prevention of hypoglycaemia and decreasing the time spent in hypoglycaemia (TBR). HCL, by regulating the delivery of basal insulin for 24 h, in addition to preventing hypoglycaemia, also allows the better management of hyperglycaemia; this aspect is perfected with advanced hybrid closed-loop systems (AHCL), which are able to automatically deliver the correction boluses as well, and, therefore, allow reducing the time spent in hypoglycemia (TBR) and hyperglycaemia (TAR), with an improvement of the time in range (TIR). Although technologies may find use in type 2 diabetes, particularly Flash Glucose Monitoring (FGM), the use of CGM and HCL is targeted almost exclusively at type 1 diabetes [2].

The components of a closed-loop system are as follows: an insulin pump, a sensor that continuously detects the glucose values in the interstitial fluid and a control algorithm that automatically modulates the insulin infusion based on the glucose values detected by the sensor. The algorithm can be integrated into the pump itself or inserted into an external device, such as a mobile phone. Therefore, the success of a closed-loop system is based on the accuracy of the sensor and the effectiveness of the infusion algorithm [1]. The most commonly used control algorithms are as follows: fuzzy logic, PID (Proportional–Integral–Derivative), and MPC (Predictive Control Model). The fuzzy logic algorithm regulates the insulin infusion based on approximate rules and empirical knowledge by simulating the reasoning of an expert diabetologist, the PID is reactive as it responds to glycaemic variations, and the MPC is proactive as it anticipates the hypoglycaemic effect of insulin, predicting glucose levels in the near future. An evolution of the MPC algorithm is represented by the DBLG1, inserted in a dedicated portable device, which, thanks to machine learning, learns day after day, thus allowing the optimisation of insulin therapy on the basis of recurring events. In addition, the CAM APS Fx algorithm, modified with MPC and machine learning, developed by the University of Cambridge, is included in an interoperable app, which allows the use of different combinations of devices currently on the market.

In addition to the algorithms used by commercially available artificial pancreas systems, systems based on self-learning which characterise the so-called open source artificial pancreas systems should be mentioned; these are "do-it-yourself" systems, as they are made by patients and therefore not scientifically validated. To create an open source system, you need a, insulin pump (usually old-generation), a CGM, and a mobile phone in which the algorithm is inserted; sometimes you also need another device that connects the three elements. Open source AID systems are represented by OpenAPS, AndroidAPS, and Loop [2].

3. CGM

Technologies and, in particular, CGM, have revolutionised diabetes management, as they have allowed a greater understanding of the disease and an improvement in treatment and outcomes. In fact, thanks to technological innovation, it has been possible to understand that diabetes is not the disease of hyperglycaemia, but of abnormal blood sugar, as well as to understand the importance of hypoglycaemia and glycaemic variability. Therefore, this has allowed us to discover that HbA1c is not sufficient for the evaluation of metabolic control, as it only represents the average blood sugar but does not describe its variability; in fact, with the same HbA1c, different variations in blood sugar can result, just as HbA1c is not representative of the time spent with glucose values in a target range (TIR), since the same HbA1c value can identify different TIRs [3].

Therefore, thanks to the CGM, a new approach has been found for the evaluation of metabolic compensation carried out through the outpatient glycaemic profile (AGP) which takes into consideration various parameters, of which the fundamental ones are HbA1c, TIR (70–180 mg/dl), and CV, or coefficient of variation; the targets recommended by the "International Consensus on the use of CGM" used to define diabetes in metabolic control are HbA1c $\leq$ 7%, TIR 70–180 mg/dl ($\geq$70%), and CV (<36%) [4].

With regard the improvement of outcomes, the use of the CGM allows increasing the TIR and reducing the CV (−3.09%) compared to the self-monitoring of glucose (SMBG) in adults and children with type 1 and 2 diabetes, as reported by a meta-analysis published in 2020 [5]. While a recent review reported a significant improvement in TIR and HbA1c with both commercial and open-source AID systems [6]. Furthermore, all this is associated with a satisfaction with the device and a lower burden related to the management of diabetes which translates into greater psychophysical well-being and an improvement in the quality of life [7,8].

4. Gender Differences in the Epidemiology of Type 1 Diabetes

Gender medicine develops in parallel with technological evolution, the former being defined by WHO as the study of the influence of biological (defined by gender) and socio-economic and cultural (defined by gender) differences on the state of health and disease of each person. Indeed, a growing body of evidence suggests that sex and gender influence the pathophysiology, incidence, prevalence, clinical manifestations, course, and response to therapy of many diseases, including diabetes mellitus [9].

In type 1 diabetes, gender differences can be easily identified: the incidence varies according to sex, age, race and socio-economic conditions, and it is the only autoimmune disease not characterised by an absolute female predominance. In fact, the incidence before the age of 15 has an M/F ratio of approximately 1:5; from puberty onwards, however, there is a decrease in the incidence in females, with a ratio that progressively reverses to approximately M/F 7:1, although females have higher Ab GADA levels and a more severe loss of beta cell function than age-matched males at diagnosis. The decrease in the incidence of type 1 diabetes in females after puberty could be due to the increase in oestrogen activity, since the hormones that characterise the various phases of the menstrual cycle and reproductive life have a role that influences the action of insulin; oestrogens seem to favour its action on peripheral tissues and progesterone seems to interfere with the action of insulin, increasing need for it. In males, however, testosterone seems to positively influence the action of insulin. Even the hormones produced during pregnancy have an impact on the action of insulin; in fact, in the first trimester there is a reduction in the requirement for insulin with a tendency to hypoglycaemia, from 18 to 24 weeks there is a progressive increase in the requirement for insulin which can even double the dose, and, finally, from the 36th week, the insulin requirement stabilises and then decreases considerably after childbirth [10].

5. Gender Differences and Acute Complications in Type 1 Diabetes

Gender differences in type 1 diabetes also concern acute complications; non-ketone hyperosmolar coma is diagnosed almost twice as often in females, and hypoglycaemia and diabetic ketoacidosis (DKA) appear to be 1.5 times more common in females as well. The increased risk of DKA may be related to body image issues leading to the arbitrary reduction or omission of insulin to promote weight loss, a condition known as diabulimia, which has a higher prevalence in females than in males (38% vs. 16%) [10].

6. Gender Differences and Chronic Complications in Type 1 Diabetes

Regarding chronic macrovascular complications, women have a higher risk of cardiovascular mortality (CVD), especially post menopause. From a first-of-its-kind meta-analysis, published in 2015, of 26 studies on gender differences in the mortality rates of 214.114 patients, it emerged that, compared to men, female mortality for all causes was 40% higher, stroke risk was 37% higher, risk of chronic kidney disease was 44%, risk of fatal CVD event was 86% higher, and risk of coronary artery disease was more than double. This meta-analysis raised, for the first time, relevant questions on gender differences in CVD risk factors in type 1 DM, on the appropriateness of treatments and on the quality of care of this population.

Gender differences in type 1 diabetes also emerge with regard to microvascular complications, as reported by data from the AMD Annals of 2021. For nephropathy, there is a higher prevalence of albuminuria in males, in which retinopathy and cigarette smoking appear to be correlated factors; in females, on the other hand, there is a more rapid progression (reduced eGFR) and a higher prevalence of normoalbuminuric chronic renal failure. Retinopathy is more prevalent in males, but blindness and reduced visual acuity are more common in females, and pregnancy seems to accelerate its progression. Neuropathy is more than twice as prevalent in females. Diabetic foot has a higher prevalence in men, but mortality is higher in women with neuropathy [11].

7. Gender Differences and Quality of Life in Type 1 Diabetes

Gender differences are also reflected in the psychological aspects and quality of life of diabetic patients. Men have less depression and anxiety, have more energy and well-being, and live more serenely with diabetes, although those with advanced disease can develop erectile dysfunction, which can cause depression and a tendency to abandon treatment; this is in contrast to women, who are more likely to hide poor adherence to therapy, knowing that insulin promotes weight gain, and while aware of the risks, they voluntarily reduce the dose, so their behaviour could give rise to feelings of guilt (cheating) [11]. A study conducted in Spain on the quality of life of adult patients with long-standing type 1 diabetes showed that the fear of hypoglycaemia has a significant psychological impact, and is independently associated with poor quality of life in both men and women. However, overall, the quality of life in women is worse than in men, probably due to a greater presence of anxious/depressive syndrome and negative impact of more glycaemic excursions. It is important to identify this category of patient and strengthen educational and psychological interventions and resort to the use of technologies with the aim of reducing glycaemic variability and improving the psychological state and, therefore, the quality of life [12].

8. Gender Differences and Advanced Technologies

The growing awareness of gender differences accompanies a huge global change in the treatment of type 1 diabetes, especially thanks to new technologies such as continuous subcutaneous insulin infusion (CSII), CGM, AHCL. A German multicentre study evaluated gender differences regarding CSII in young and adult patients. In the young group, the same percentage of males and females using the CSII was found at the start (2.6%), but after nine years the prevalence of using the CSII became higher in females (F 53%, M 45%). In the adult group, the difference was evident right from the start, with a higher prevalence of use in the female sex (F 28%, M 18%), which increased progressively after fourteen years (F 49%, M 30%) (Figure 2). The reason why females use CSII more than males seemed to be the worse metabolic compensation; moreover, females showed greater acceptance for CSII. Regarding the metabolic compensation, in the young group at the start, the Hb1Ac was slightly higher in the females (F 8.3%, M 8.15%); after nine years, there was a significant reduction in the gap (F 8.07%, M 8%). In the adult group, males started with 8.4%, reached 8.72% after six years, and returned to 8.43% at the end of the study. Females followed this trend in parallel, showing constantly lower values: 8% at the start with a maximum value of 8.4%, and finally 8% at the end of the study (Figure 3). The daily insulin requirement in the young group was initially higher in males (F 0.77 U/kg, M 0.82 U/kg) then the difference completely disappeared at the end of the study (0.90 U/kg). In the adult group, the same dosage of insulin was initially found for both sexes (0.67 U/kg); over the years, the males maintained a higher dosage until it became almost the same as the females' dose at the end of the study (F 0.69 U/kg, M 0.71 U/kg) (Figure 4) [13]. The results of the German study contradict the Italian data from AMD Annals 2021, according to which in the adult population of women are 30% less likely to have an HbA1c $\leq$ 7% than men, and are more frequently treated with CSII (15.5% vs. 11.1%), even if the percentage of use in both sexes is much lower than in Germany. The analysis of the metabolic compensation

(HbA1c ≤ 7%) based on the type of treatment shows an improvement in both sexes, but less so for women: 24.2% in MDI and 30.9% in CSII reach the HbA1c target, while for men the figures are 30.3% in MDI and 35.5% in CSII. Some population studies conducted in different continents (Australia, North America, and Europe) confirmed Italian data. In women with type 1 diabetes, hormonal variations can affect glycaemic variability and, even worse, metabolic compensation, but also lead to psychological differences and the adaptation and acceptance of the pathology; in fact, depression and the burden of the disease prevail in the female sex. In reality, there are multiple factors that can influence metabolic compensation and condition gender differences: biological factors (genetic, epigenetic, hormonal, and biological risk factors), non-biological factors (culture, lifestyle, environmental factors, socio-economic, etc.), and comorbidities (anxiety, depression, physical limitations, cognitive deficits, and other pathologies) (Figure 5) [11]. The AMD Annals themselves also highlight gender differences in the management of other CV risk factors: men are likely to have hypertension and be smokers, while among women there is a higher percentage of obesity and LDL hypercholesterolemia; this situation is not dissimilar from that of ten years ago [14]. Italian data are in line with those of the rest of Europe. An observational study of adults with type 1 diabetes in the Netherlands showed worse metabolic compensation (HbA1c ≤ 7%) in women compared to men (21.1% to 26.6% vs. 20.9% to 30.4%), and found that a higher proportion of women use CSII (30.3% vs. 17.3%). Furthermore, women have a higher risk of hypoglycaemia, are more likely to be overweight/obese, are less likely to be treated with antihypertensive, lipid-lowering, and antiplatelet drugs, and those on treatment reach the target lipid profile less frequently. Men, on the other hand, have poor blood pressure control and are more likely to be smokers. Also, in this case, gender disparities in diabetes care and in the educational path have not been demonstrated, but it is believed that the differences could be attributed to multiple factors: biological, behavioural, psychological, etc. [15]

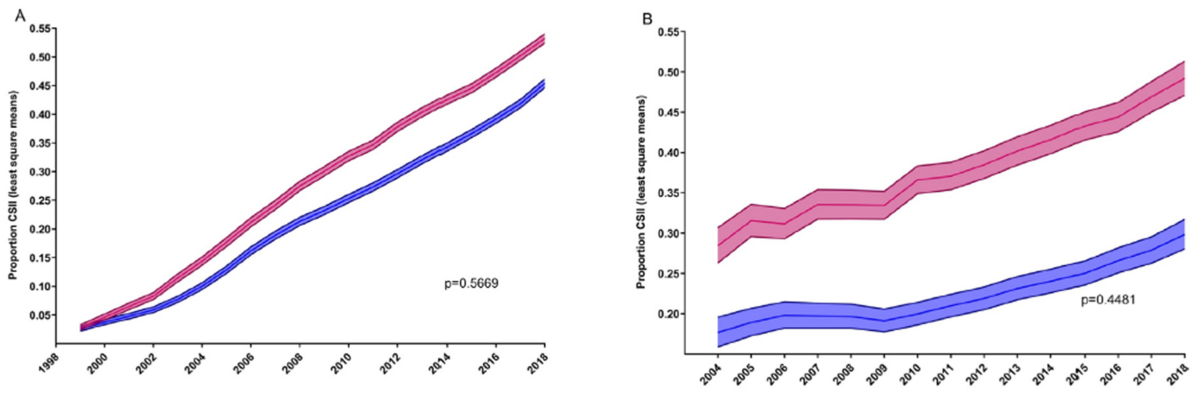

Figure 2. Use of CSII in males (blue) and females (red); (**A**) youth, (**B**) adults.

In people with type 1 diabetes, technologies facilitate the performance of physical activity and, above all, the management of hypoglycaemia. The reduction in basal insulin, the temporary basal rate, the reduction in the prandial bolus, and the intake of carbohydrates allow the prevention of hypoglycaemic events. A recent study found gender differences in the strategies adopted to prevent hypoglycaemic events related to exercise; a higher percentage of men eat carbohydrates before (M 70.8%, F 62.1%) and during (M 56.5%, F 42.7%) physical activity, while the frequency of insulin reduction is similar in both genders (meal bolus reduction: M 55%, F 57.3%; baseline reduction: M 8.1%, F 8.8%), although women always prefer to reduce their insulin rather than consume carbohydrates (Figure 6) [16].

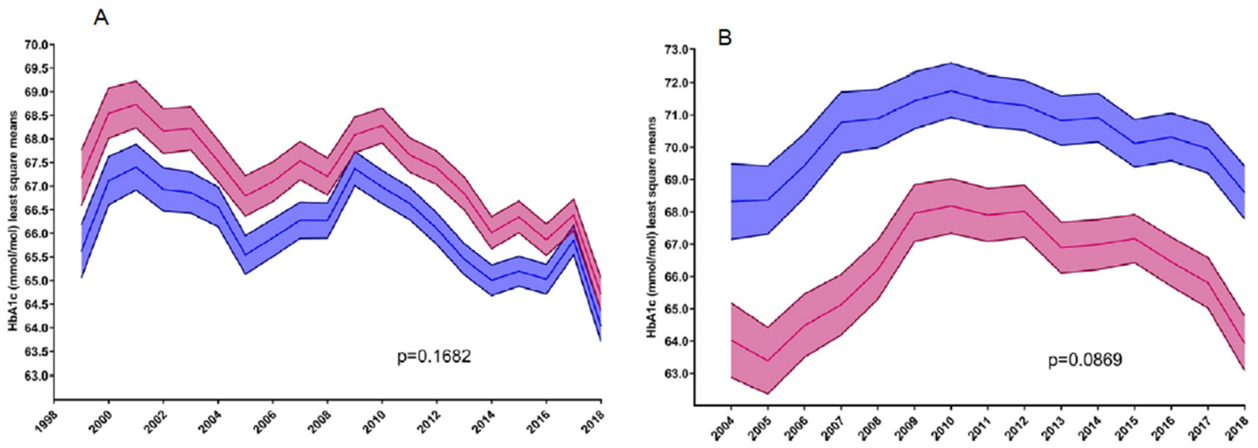

Figure 3. Metabolic compensation in CSII in males (blue) and females (red); (**A**) youth, (**B**) adults.

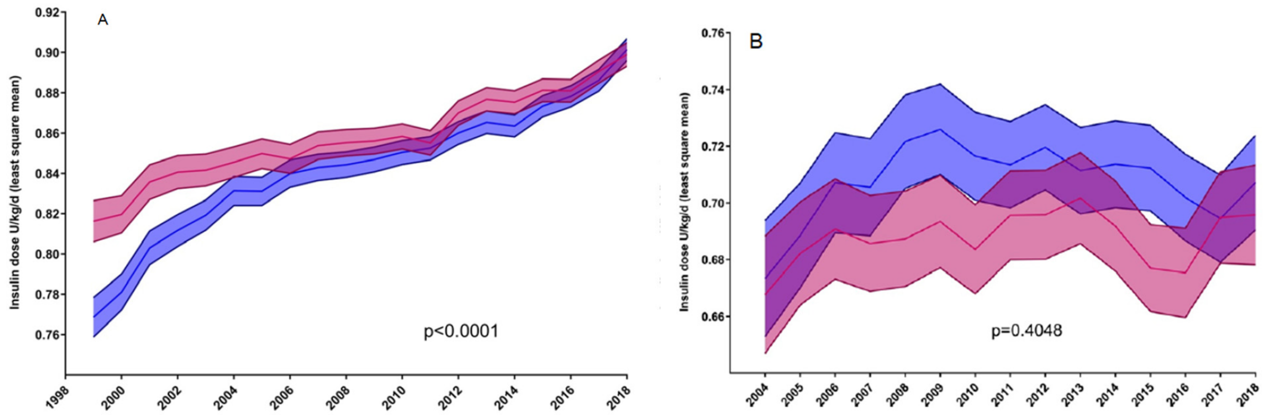

Figure 4. Daily insulin dose in CSII in males (blue) and females (red); (**A**) youth, (**B**) adults.

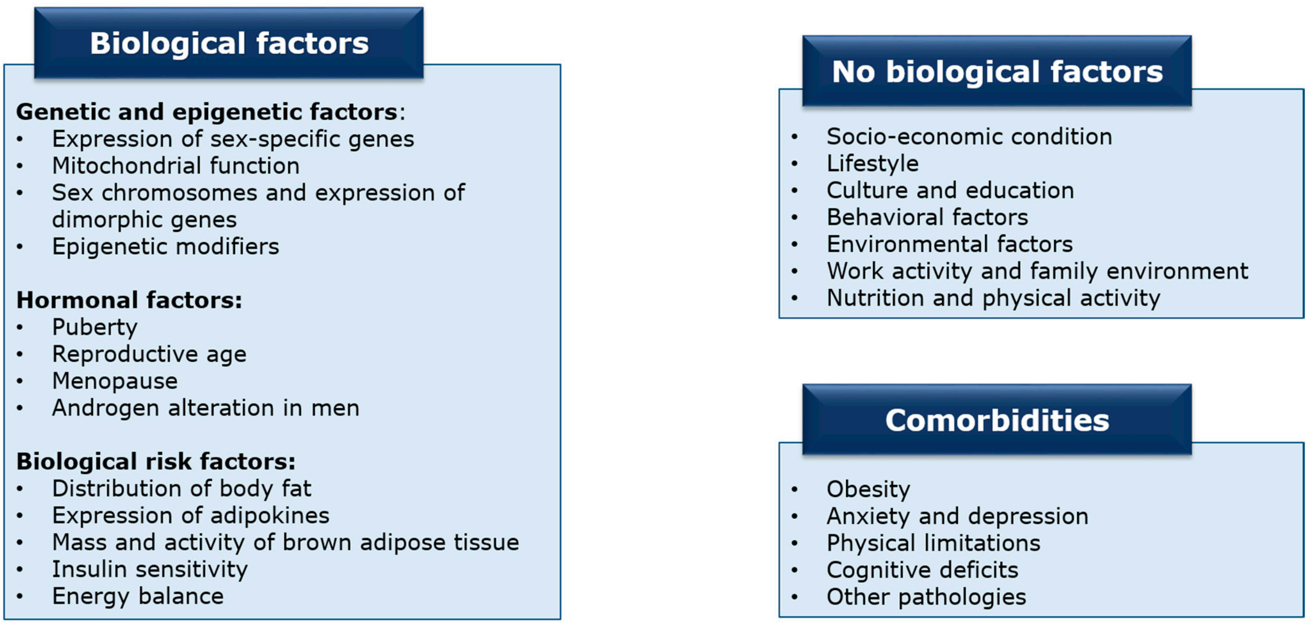

Figure 5. Factors influencing gender differences in type 1 diabetes.

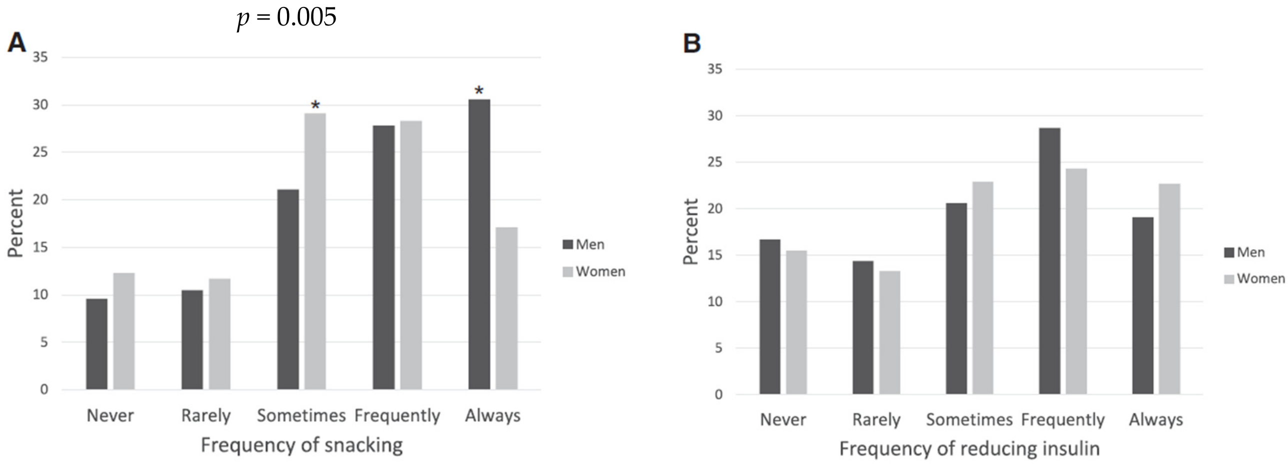

Figure 6. Management of hypoglycaemia related to physical exercise in CSII. (**A**) Frequency of snacking. (**B**) Frequency of reducing insulin, *: It is significant difference between Groups related to "sometimes" and "always".

9. Technologies and Pregnancy

Various technologies have made it possible to improve the management of type 1 diabetes in pregnancy. The CONCEPTT study (2017), a landmark randomised controlled trial of the use of CGM in diabetic pregnant women or women planning a pregnancy, found no differences in hypoglycaemia between the CGM and SMBG groups, but a reduction in the TAR was found in the CGM group, which corresponded to an increase of several hours in the TIR; furthermore, there was an improvement in foetal outcomes (birth weight, neonatal hypoglycaemia, etc.) associated with the use of the CGM. In 2018, a meta-analysis of randomised studies in pregnant women found better glycaemic control, reduced insulin requirements, and improved foetal outcomes in those on CSII compared to those on multi-injection (MDI). Additionally, CSII use during delivery was associated with higher TIR than switching to an IV infusion of insulin. Also, several studies on HCL demonstrate a TIR about 69% higher than SAP in pregnancy and during delivery, with reduction in TBR. Currently, the only commercially available AHCL approved for use in pregnancy is CamsAPS FX [17].

10. Conclusions

Although sex and gender differences have emerged regarding the prevalence of use and adherence to therapy with advanced technologies, the perceived benefits for both sexes were better glycaemic control, the prevention of long-term complications, better quality of life, and reduced mental burden related to diabetes. Annoyances and limitations have included unexpected tasks for the user, difficulty wearing the system, concerns about controls, and remembering limitations of diabetes. However, patients are willing to accept some negative aspects if they perceive benefits for their health and quality of life. It is the duty of clinicians to select candidate patients for the use of technologies and to provide them with an accurate view of the positive and negative aspects to help them manage expectations, as individuals who are properly informed and educated about technologies will be the ones most likely to persevere with their use and reap their long-term benefits. Meanwhile, it is necessary to deepen the knowledge about the relationship between sex-gender differences regarding diabetes to allow the phenotyping of the patient, the personalisation of therapy, and a move towards precision medicine.

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