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Diabetes and lipid disorders

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Abstract. Glucose homeostasis is impaired in girls and women with Turner syndrome. A decreased insulin sensitivity as well as a reduced β -cell function seems to play a role. Impaired oral glucose tolerance test is found in up to 78% of study populations. An epidemiological study have found a relative risk of type 1 diabetes of 11.6 and type 2 diabetes of 4.4 in Turner syndrome. © 2006 Elsevier B.V. All rights reserved.

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1. Introduction

The original description of Turner syndrome (TS) by O. Ullrich or H.H. Turner did not include a description of adults and hence diabetes and lipid disorders were not described. However, during recent years, it has become increasingly clear that type 2 diabetes and perhaps also type 1 diabetes occur more frequent in women with TS and at a quite young age. The presence of lipid disorders is somewhat more debatable and has been shown to be present by some but not by others. Here we present the available evidence for both diabetes and lipid disorders.

2. Prevalence

Early reports of increased frequency of diabetes in TS are found, and in the sixties impaired glucose tolerance was found in 60% (44% if aged below 50) [1]. We found an increased relative risk (RR) of developing both type I diabetes and type II diabetes in an epidemiologic study [2] (Fig. 1).

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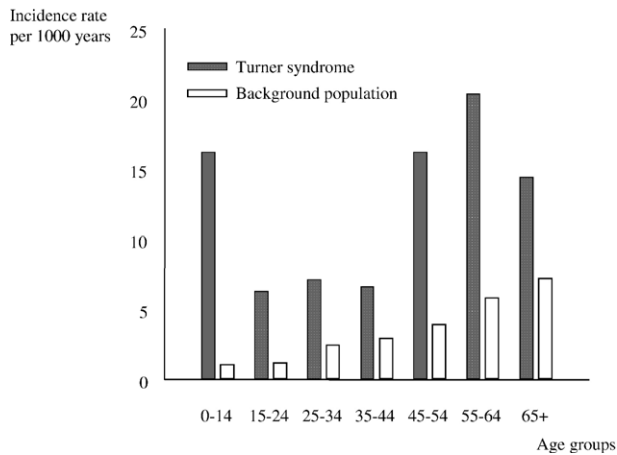


Fig. 1. Relative risk of endocrine disease in the TS population by age: type 1 diabetes (RR=11.6), type 2 diabetes (RR=4.4), thyroiditis (RR=16.6) and hypothyreosis (RR=5.8).

In a British epidemiologic study, Price et al. found increased mortality, but did not report an increased frequency of diabetes [3]. And likewise a later British epidemiologic study did not find an increased frequency of diabetes as a cause of death [4]. We have recently found diabetes to be a contributory cause of death in about one fourth of the cases, indicating that the increased frequency of diabetes leads to an increase in mortality (unpublished observations).

3. Glucose homeostasis

The glucose homeostasis in TS has in several studies been shown to be impaired in both TS girls [5,6] and women [7–9]. In adolescents, it has been found to improve compared to controls [6], probably because the normal relative insulin resistance seen during puberty is absent.

Fasting hyperinsulinemia are found by some [5,10], not by others [6,7,11,12], and generally fasting glucose levels are not significantly different from controls in the available studies (age less than 50 years) [7,10,11].

When performing an oral glucose tolerance test (OGTT) impaired glucose tolerance (IGT) has been found in 25–78% [6,7,11–13] of adult TS. In addition to higher glucose levels, the insulin response is increased and some find a delayed insulin peak during an OGTT [12].

Several studies have by varying methods described different aspects of glucose intolerance, trying to distinguish the role of insulin sensitivity and β -cell function.

We performed an intravenous glucose tolerance test (IVGTT) in 24 TS and age-matched controls, and found similar insulin sensitivity and glucose effectiveness by minimal modelling in TS and controls. A relative ‘first phase insulin response’ impairment which could be viewed as an inappropriately low β -cell response was found (Fig. 2), as well as an increased level of free fatty acids during the OGTT [7]. We later studied hypertriglyceridemia during an OGTT, which has previously been linked to insulin resistance in healthy

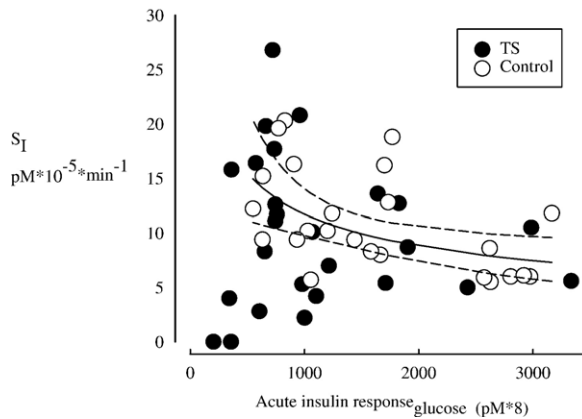


Fig. 2. Insulin sensitivity index (S_I) and acute insulin response measured as area under the curve during first 8 min of an IVGTT.

relatives of type 2 diabetics [14], but found triglyceride levels not significantly different from controls in TS independent of hormone replacement therapy (HRT) (unpublished data).

We extended our study of glucose homeostasis and found slightly reduced insulin sensitivity in 10 TS women by renewed analysis of OGTT data [11]. Furthermore, in muscle biopsies, we found an increased size of type IIa fibers (but not type I and type IIx). Physical fitness was evaluated and a reduced physical capacity was found. This combined with enlarged type IIa muscle fibers could indicate diminished oxygen and substrate supply for metabolic processes, and could thus be indicative of a prediabetic state [11]. Thus, a state of normal fasting glucose and insulin levels, but compromised glucose metabolism during stimulation seems to be present, including elevated 2 h glucose, and thus presumably also postprandial hyperglycemia.

Choosing a control group for studies of girls and women with TS is problematic. Matching on height is almost impossible and will inevitably lead to differences in other aspects of body composition. Salgin et al. tried to overcome some of these problems in a study of 16 TS women and controls, with no significant difference in weight, but a 16 cm reduction in height in the TS women. However, body composition determined by DEXA showed significant differences in whole-body fat mass and truncal fat mass, even after correction for height. The authors tried to adjust for differences in whole-body fat mass or whole-body fat mass/fat free mass ratio when calculating whole-body insulin sensitivity. Both before and after adjustment, this was significantly lower in TS. The authors concluded that the increased insulin resistance in TS is independent of measures of body composition and may represent an intrinsic defect related to their chromosomal abnormality [15].

Others have resorted to inclusion of controls matched on gonadal insufficiency [13,16] in this way matching on one of the other characteristics of Turner syndrome. Bakalov et al. compared TS to age-matched women with premature ovarian failure (POF) and healthy controls (TS: $n=25$, POF: $n=33$). Similar baseline glucose levels were found in the TS and POF, but 2 h glucose levels were more than 50% increased in TS. 36% of TS had IGT, none in

the POF group. An IVGTT was performed on TS and healthy controls ($n=33$). This revealed a reduced glucose stimulated insulin release in TS, increasing with age and higher in TS with IGT by OGTT, but also present in younger women with normal IGT, corroborating earlier data [7]. The authors suggested the presence of β -cell insufficiency in TS and the fact that this was not present in the POF women indicated that it was a feature of the syndrome (X haploinsufficiency), and not other factors related to gonadal insufficiency [13].

Nevertheless, due to the number of specific stigmata of the syndrome, it is impossible to match any control group on all the stigmata that characterizes women with TS.

HRT has been found to significantly reduce fasting glucose [17] and fasting insulin [7,17]. Fructosamine, as a measure of the average level of glucose during the preceding 14 days and fasting plasma insulin, was reduced significantly during HRT compared with no treatment, indicating improved glycemic control. Insulin sensitivity was unchanged (assessed using an IVGTT with minimal model analysis), while more subjects during an OGTT had impaired glucose tolerance [7]. Despite this, there was no significant change in glucose and insulin response (measured as area under the curve) or the 2 h glucose level. An increase in fat free mass and physical fitness was also seen on HRT, both factors that improve glucose homeostasis [7]. So despite the fact that an increase in IGT is seen during HRT, other parameters indicate an improvement in glucose homeostasis. There is a serious problem in comparing the effect of HRT on insulin sensitivity in postmenopausal populations, given the inevitable age difference with a TS population. Furthermore, most women with TS suffer from extreme premature ovarian failure, with no or only a very short-term period of natural menstruations [18]. Many females with TS are naive to the effects of female sex hormones, although some of them experience natural or semi-natural puberty. In one study of young women with POF, who could be compared to women with TS with respect to age, HRT has been shown to diminish insulin sensitivity (minimal model derived insulin sensitivity) [19]. Also Duncan et al. studied a population of relatively comparable women but found no effect on insulin sensitivity [20]. There are no very long-term controlled studies of the effect of HRT on glucose metabolism in patients with TS or in otherwise healthy women of a comparable age.

Available data indicates that a large proportion of women with TS have an abnormal glucose tolerance and inappropriate high levels of circulating insulin without and during replacement with sex hormones, which could indicate a deranged β -cell function. Thus, during longer-term treatment with sex hormones an improvement in the indices of carbohydrate metabolism may take place; perhaps partly through the expedient effects of sex hormone replacement on physical fitness, body composition and blood pressure.

Conclusively, it should be noted that there is a need for attention being paid to the increased risk of impaired glucose homeostasis and diabetes in TS. Recommendations for diagnosis and treatment of diabetes in any patient should be followed. However, yearly screening of fasting glucose is recommended and on suspicion an OGTT should be performed.

4. Glucose metabolism during GH treatment

Special attention has been paid to glucose metabolism during growth hormone (GH) treatment in TS girls. Several studies have looked at this. The age range of the girls in the following studies is 2–32 years.

Fasting glucose levels have been found unchanged during GH treatment in most studies [21–26], but increased in others [27], while a dose response study only found increased fasting glucose in the group that received the highest GH doses [25]. The values returned to baseline values after termination of GH [25].

Most studies find a significant increase of glucose levels (OGTT) during GH treatment [21,27–29]. Other studies find similar glucose levels despite decreased insulin sensitivity (ISI_{comp}) before and after GH [23–25], with a return to pre-treatment levels 6 months after GH discontinuation [28].

Insulin levels, both fasting and as an OGTT response, increase during treatment [24–27,30]. A study of seven girls during an hyperglycemic clamp showed an increase in overall insulin response as well as first and second phase response in TS which increased further during GH treatment [26]. One explanation could be reduced insulin sensitivity. The insulin levels decrease after termination of GH, but do not return to levels as low as before treatment [21,25,28]. This could be an irreversible effect of GH, but could also be due to the fact that both fasting insulin and area under the curve for insulin (AUC_I) increases with age, particularly during adolescence [31].

Insulin sensitivity is reduced compared to healthy controls prior to treatment [32] is further reduced during treatment [24,27,32,33], and then increases after the cessation of treatment, returning to the level before GH treatment [24]. GH generally reduces insulin sensitivity in the first 6–12 months of treatment, where after it stabilizes [32]. The insulin sensitivity returns to pre-treatment levels in most studies [28].

It has been speculated that the GH effect on body composition with increased lean body mass and decreased fat mass, improves insulin sensitivity, and can explain the stabilisation or maybe even improvement of insulin sensitivity [29,34]. Improvements in body composition are seen after just 2 months of GH treatment [27].

The number of TS with IGT does not seem to increase significantly during treatment [22,32], and HbA_{1c} seems unchanged [22] or even decrease during GH treatment [25].

Despite the fact that most effects on the glucose metabolism seems to be reversible after cessation of GH treatment, the long-term effects of the GH induced hyperinsulinism and insulin resistance are not known.

There have been reports of girls developing diabetes during GH treatment [32] or 50 months after termination of GH and Oxandrolon treatment [21].

5. Lipids

The risk of ischemic heart disease has been found to be elevated in TS ($RR=2.1$) [2]. Contributing factors could be congenital heart disease, hypertension and impaired glucose homeostasis. An atherogenic lipid profile could also be one. Several studies have found no difference compared to controls in lipid metabolites [7,23,35–37], while others find increased HDL levels [37], but some find reduced HDL levels [15]. Several find increased triglyceride levels [11,15,38]. Higher triglyceride levels could be a consequence of hyperinsulinaemia and obesity [39]. However, a relatively large study of TS girls (5–14 years) found elevated cholesterol levels, but similar triglyceride levels in adolescent TS compared to controls [40]. One study found a significant decrease in HDL cholesterol

during HRT [7], others found no difference in lipid profiles in TS with or without HRT [17,36].

Total cholesterol, LDL- and HDL-cholesterol and triglycerides were all found significantly increased in nonobese TS compared to nonobese, age-matched women with POF with similar relative body fat and truncal fat determined by DEXA. This could indicate that also the unfavourable lipid levels found in this study may be caused by X haploinsufficiency of unknown genes [41].

Indications of genomic imprinting playing a role in visceral adiposity and lipid profile has been found in a smaller study of TS grouped by monosomy for maternal inheritance of the X chromosome (X^M) or paternal inheritance (X^P). Both triglyceride, LDL-cholesterol, total abdominal fat and visceral fat was significantly increased in the X^M group compared to the X^P group. HDL cholesterol was similar in the two groups. The X^M group seems to have an atherogenic lipid profile more similar to that seen in men [42].

GH treatment seems to reduce total cholesterol levels and LDL levels, but increase HDL and triglyceride levels [28,37,43] although no changes were found by others [27,44].

6. Conclusion

While the available data on glucose homeostasis is uniform and easily interpretable, and show a high frequency of type 2 diabetes, impaired glucose tolerance and β -cell inadequacy, suggesting an influence of haploinsufficiency of genes on the X chromosome, the data on lipid metabolism is more heterogenous. The results regarding lipids may be the result of different control groups in different studies, and more studies are needed to determine whether or not lipid metabolism is really altered in TS.

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