Klinefelter syndrome, insulin resistance, metabolic syndrome and diabetes.

Review of literature and clinical perspectives.

Andrea Salzano*[1,2], Roberta D'Assante*[3], Liam M. Heaney[2], Federica Monaco[1], Giuseppe Rengo[1], Pietro Valente[1], Daniela Pasquali[4], Eduardo Bossone[5]; Daniele Gianfrilli[6], Andrea Lenzi[6], Antonio Cittadini[1], Alberto M. Marra[3], Raffaele Napoli[1].

*These authors equally contributed

[1]*Department of Translational Medical Sciences, Federico II University School of Medicine, Naples, Italy*

[2]*Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Glenfield Hospital, Leicester, UK,*

[3] *IRCCS S.D.N., Via Gianturco 113, 80143, Naples, Italy*

[4]*Department of Neurological, Metabolic, and Geriatric Science, Endocrinology Unit, University of Campania "Luigi Vanvitelli", Caserta, Italy*

[5]*Department of Cardiology and Cardiac Surgery, University Hospital "Scuola Medica Salernitana", Salerno, Italy*

[6] *Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy*

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Corresponding Author:

Prof. Antonio Cittadini
Department of Translational Medical Sciences
Federico II University School of Medicine
Via Pansini 5,
80131 Naples, Italy.
E-mail address: antonio.cittadini@unina.it

Abstract

Klinefelter syndrome (KS), the most frequent chromosomic abnormality in males, is associated with hypergonadotropic hypogonadism and an increased risk of cardiovascular diseases (CVD). The mechanisms involved in increasing risk of cardiovascular morbidity and mortality are not completely understood. Insulin resistance, metabolic syndrome, and type 2 diabetes are more frequently diagnosed in KS than in the general population; however, the contribution of hypogonadism to metabolic derangement is highly controversial. Whether this dangerous combination of risk factors fully explains the CVD burden of KS patients remains unclear. In addition, testosterone replacement therapy only exerts a marginal action on the CVD system. This review summaries the current understandings of the complex relationship between KS, metabolic syndrome and cardiovascular risk in order to plan future studies and improve current strategies to reduce mortality in this high-risk population. Since fat accumulation and distribution seem to play a relevant role in triggering metabolic abnormalities, an early diagnosis and a tailored intervention strategy with drugs aimed at targeting excessive visceral fat deposition appear necessary in patients with KS.

Introduction

Klinefelter syndrome (KS) is an aneuploidy characterized by a supernumerary X chromosome and hypergonadotropic hypogonadism [1]. The estimated prevalence of 1 case per 660 newborns, increasing to 3–4% among infertile men and 10–12% in azoospermic men, makes KS the most common abnormality of sex chromosomes [2-4]. Clinical features of the syndrome vary broadly [5-9], but the hallmark of KS remains infertility [5] with most of cases remaining undiagnosed until the attempt to conceive [10]. While about 85% of KS is due to one single additional X chromosome (47,XXY), the remaining 15% displays multiple aneuploidies (48,XXXY; 48,XXYY; 49,XXXXY) causing development of a much more complex phenotype [11]. This includes mental retardation that is no longer considered a feature of classical KS [12]. For this reason, aneuploidies with more than 47 chromosomes should be considered a distinct condition [5,11].

Compared to the general population, patients with KS show higher all-cause and cardiovascular disease (CVD) mortality [13-17]. Data from recent large registry-based studies reported a significant increase in mortality risk by 40% (hazard ratio (HR) for all-cause mortality = 1.40; HR cardiovascular mortality = 1.41) [14] with a standardized mortality ratio (SMR) of 1.5 [15], corresponding to a significantly reduced median survival of 2.1 years. Patients with KS are more frequently insulin resistant, obese and prone to develop type 2 diabetes mellitus (T2D) [18,19], a condition considered a CVD equivalent. The onset of T2D in patients with KS is a turning point in worsening of the CVD risk profile. With this in mind, we explored and reviewed the relationship between KS and metabolic abnormalities, focusing on diabetes mellitus and its implications on the increased CVD mortality observed in KS patients.

Insulin-resistance and metabolic syndrome in Klinefelter syndrome

According to the National Cholesterol Education Program - Adult Treatment Panel III (NCEP- ATP III) criteria [20], metabolic syndrome (MS) clusters multiple CVD risk factors. In

2005, the International Diabetes Federation (IDF) reviewed these criteria which lead to an increased estimated prevalence of MS [21]. These criteria have now been reconciled in a joint interim statement to more precisely characterize MS [22]. Furthermore, a definition of pediatric MS, designed to be closely analogous to ATP III, was described by de Ferranti et al. in 2004 [23].

As summarized in Table I, the prevalence of MS in patients with KS appears higher than in the general population, with data suggesting a 4-fold higher prevalence of MS in untreated KS than controls (46% vs 10%) [24]. In the same study, patients with KS presented with insulin resistance (IR - measured by the HOMA index), low androgens and low HDL cholesterol concentrations. KS was consistently associated with increased total body fat, however surprisingly, testosterone replacement therapy (TRT) did not modify fat tissue distribution or insulin sensitivity (IS) (Table I and Fig.1). Similar findings in respect to lipid and testosterone levels and MS were described in a subsequent study [25]. More than one third of patients with KS were identified as IR when tested by the euglycemic hyperinsulinemic clamp [26]. In this elegant study, serum testosterone levels were independently associated with insulin-mediated whole body glucose uptake, suggesting hypogonadism might be responsible for IR in KS patients [26]. In a smaller study, Pei and colleagues confirmed that IR, measured by insulin area under the curve (AUC) during a 75-gr oral glucose load and insulin suppression test, was constantly elevated in patients with KS [27]. Interestingly, plasma glucose at the steady state was inversely correlated to testosterone levels, again pointing toward a role for androgens in the IR of KS. In a study performed by ourselves, we described a prevalence of 49% for MS in 69 untreated KS patients, compared to 10% among controls [28]. In the 48 patients prescribed TRT, the prevalence of MS during the 3-year follow-up period was unaltered and remained higher than that observed in a group of 21 men with hypogonadotropic hypogonadism treated with testosterone [28]. These data indicate that KS patients are more insulin resistant, have increased body fat and lower levels of HDL, and show an increased prevalence of MS when compared to a control population. Also, circulating testosterone appears related to IS, however, the effect of TRT does not reverse MS. In the general population

and in experimental models, a clear bidirectional relationship between testosterone and IS exists [29-31]. Low testosterone levels are associated with increased IR [31] and the onset of IR may influence testosterone levels [32,33] (Fig. 1). Treatment of hypogonadal men with testosterone improves metabolic risk factors and IR in some, but not all studies [34]. Compared to other types of hypogonadism, TRT has shown to not improve body fat distribution or IR in KS [24,28], suggesting either a possible“ hormonal resistance”, consistent with the accompanying elevated LH [10], an increased aromatization [35], or alternatively, that the androgens are not involved in the metabolic impairment of KS. The chromosomal abnormality may act through additional mechanisms in triggering IR, differential body fat distribution and MS (Fig. 1), despite inactivation of the extra X chromosome. From this point of view, the study of prepubertal adolescents with KS offers an important opportunity. Although they carry the chromosomal abnormality of the syndrome these patients have similar, prepubertal, circulating testosterone and gonadotropin plasma levels to age-matched healthy controls. Therefore, the independent, non-hormonal, role of chromosomal abnormalities can be better ascertained at this age [10,36]. In a group of 89 boys between 4 and 12 years, 30% had a waist circumference >90th percentile (vs 21% matched controls), 24% were insulin resistant and 7% had three age-matched criteria for the diagnosing MS [37]. In a more recent cohort of 93 pre-pubertal boys with KS [38], 80% had ≥1 feature of MS and 11% had ≥3 features of MS. In the same cohort of patients, authors performed a 2-year double-blind placebo-controlled trial of oral oxandrolone (Ox) [39]. This showed a modest improvement in some features of MS (systolic BP, fasting blood glucose, and triglycerides) and in body composition although, after adjusting for age and baseline measures, the only significant change was a reduction of triglycerides. In particular, these changes were more strongly associated within the subgroup of patients who remained prepubertal throughout the 2-year study. In addition, the treatment did result in bone age advancement and lowering of HDL cholesterol. Of note, total body fat, assessed by bioelectrical impedance analysis, was found higher in infants and adolescents with KS, independently of BMI, age, and testosterone concentration. Thus, KS patients

seem to display an accumulation of truncal body fat and lower lean body mass (28). Iwatsuki et al. demonstrated that LH and FSH, but not testosterone, inversely correlate with BMI in KS but not in men without KS [40]. Aksglaede et al. comparing eighteen untreated and six testosterone-treated KS boys to a group of normal aged-matched controls, found an increased fat body mass, but normal lean body mass, in patients with KS [41]. Overall, these data suggest that an unfavorable metabolic profile is already present in children with KS, although testosterone levels are not different from their healthy peers.

Bojesen et al. showed that in patients with KS, as for the general population, truncal body fat is associated with IR [22]. Interestingly, when metabolic data from patients with KS were adjusted for truncal body fat, the correlation with hypogonadism was lost, suggesting that the effects of androgens on IS was mediated by fat distribution. Recently, in a group of ten obese KS patients with T2D and erectile dysfunction (ED), the addition of metformin and liraglutide induced weight loss and improved erectile function in the patients in which TRT alone was insufficient to achieve serum T levels in the range of healthy men. Furthermore, the patients were able to reach glycemic targets and to lower weight, leading to a considerable improvement of ED [42].

Recently, a prevalence of obesity in Korean men with KS of 42.6% was reported, with testosterone level as an independent risk factor for obesity and hyperglycemia [43]. On the other hand, obesity in KS is not just a bystander, since only KS patients with obesity have a high incidence of hyperglycemia, low testosterone level, and elevated LH and FSH levels [44].

A very intriguing relationship exists between KS, MS and the increased risk of thromboembolic disease [18,43,45,46]. MS is associated with a low-grade chronic inflammatory status. Recently in a cohort of 26 testosterone treated KS patients, serum levels of C-C motif chemokine ligand 2 (CCL2), the major chemokine released by the monocytes and macrophages and associated with IR, along with prevalence of MS (50%) and IR were higher than in controls. However, when the group of patients was divided according to the presence of MS, hormone concentrations, adiponectin, CCL2, and CXC motif chemokine 10 (CXCL10) levels were similar.

Therefore, the effects on CCL2 circulating plasma levels seen in KS were not mediated by MS or body fat distribution, rather to other putative mechanisms operating in KS itself. In fact, the observation that in patients with KS testosterone correlated positively with CCL2 contrasts with *in vitro* data where testosterone reduces the secretion of several cytokines and chemokines, including CCL2, from peripheral blood mononuclear cells [47]. Consistently, when adult men are acutely deprived of testosterone, CCL2 levels increase. These data suggest that a proinflammatory status in KS may also account for some dysfunction of Leydig cells [47,48] and that macrophage infiltration into an expanded adipose tissue might be involved in the development of MS in KS [49].

Diabetes mellitus in Klinefelter syndrome

Type 1 diabetes mellitus (T1D) accounts for between 5 and 10% of all diabetes cases and is due to autoimmune destruction of the pancreatic beta-cells [50]. Autoimmunity is also frequent in KS. Interestingly, a recent study demonstrated that immunoreactivity directed against diabetes-specific autoantigens was significantly increased in KS (8.2%) than matched controls, but the autoantibody endocrine profile of untreated and treated KS patients was not different [51]. Bojesen et al. [13] reported a 2.5-fold increased risk of T1D in KS when compared to the general population. Since the first study evaluating the prevalence of T2D and KS performed by Langeron et al. in 1958 [52], many reports [53-66] have documented the association of KS with T2D (Table II). An abnormal oral glucose tolerance test can be detected in more than one third of KS patients [56], leading to the suggestion of considering KS a "*prediabetes"* [57]. The prevalence of overt diabetes in KS is estimated higher than 10% in various studies [59-65,67]. Interestingly, the prevalence of diabetes is increased also in parents of siblings with KS [61], suggesting a familiar cluster of the metabolic abnormalities. Of interest is the observation that the prevalence of diabetes is even higher (up to 57%) in patients with the more severe karyotypes (48, or 49 chromosomes), pointing to an additive role of the supernumerary X-chromosomes in the onset of T2D in KS [62]. Our group reported a prevalence of diabetes slightly higher than in the general population [28].

Recently, Han et al found a prevalence of 26% of "prediabetes" and of 13% of diabetes in 375 Korean KS patients. Despite no difference observed for the prevalence of diabetes between obese and non-obese KS patients, prediabetes was more frequent in the obese KS group [43].

The course of diabetes in patients with KS has some peculiarities compared to the general population. In particular, KS patients develop the disease earlier in life (onset around 30 years) and with an associated BMI lower than what is usually observed in non-KS patients with T2D. Finally, insulin treatment appears less effective in achieving metabolic control [60], but compliance might be a confounding issue. As for MS, TRT does not halt the onset of diabetes in KS, nor changes its severity [45]. Data from large registry-based studies showed a HR of 2.21 for T1D and 3.71 for T2D in KS [13-17]. In a cohort of 781 Danish KS patients, a 60% increase in the risk of death due to T2D was reported [13]. However, such reported risk might well be underestimated, since T2D is not usually recorded as a primary cause of death. Swerdlow et al. extracted data from a cohort of 4806 UK-based patients with KS diagnosed between 1959 and 2002 [15]. The authors calculated the SMR related to diabetes at 5.8 and showed that the contribution of diabetes as the cause of death in this population increased with age. In addition, no differences were found when the classic XXY karyotype was compared with other chorotypes or mosaic, although abnormal glucose tolerance was more frequently detected in classical KS [57].

The clinical response to TRT might be influenced by the polymorphism of the gene encoding for the androgen receptor on the X chromosome. A certain number of CAG repeats (CAGn) characterizes this gene and the number of CAGn is inversely associated with androgen sensitivity: the higher the CAGn, the lower the sensitivity to androgens, suggesting a possible role in the clinical response to testosterone therapy in KS [67]. Bojesen and collaborators, studying a group of 70 patients, supported the concept that CAGn polymorphism affects the phenotype of KS [68]. However, in this cohort, the CAGn repeats influenced height, arm span, total cholesterol, hemoglobin, and red blood cell count of KS patients, but not the response to TRT. Although testosterone might potentially affect metabolism through several mechanisms [69-72], TRT in KS

does not seem directly affect glucose metabolism.

Diagnostic and therapeutic perspectives

Although KS patients are more insulin resistant and have an increased risk of developing MS and T2D, they are not listed among groups requiring a more frequent screening for metabolic impairment. Since T2D severely impacts mortality in KS and current standards of TRT failed to prove effective in this respect, an open issue remains on how to prevent or treat diabetes in KS patients. Specifically, no information is available within current guidelines regarding a particular strategy to be used in the prevention of diabetes or its complication in this particular group of patients [73]. In contrast, it is suggested that in any individual older than 45 years and with a condition of IR, such as polycystic ovary syndrome, severe obesity or acanthosis nigricans, should be tested for diabetes. We propose to add KS as a condition requiring early screening, maybe even earlier than 45 years, given the early onset of T2D in KS patients.

Counseling from an early age regarding a healthy diet and regular exercise is imperative for KS patients. As suggested by Davis et al [74], a screening for dyslipidemia with a fasting lipid panel at age 9 to 11 years and after puberty is completed (or sooner if additional risk factors are present) could be a good strategy to recognize MS or its features as soon as possible. This assessment needs to be repeated after puberty, and it is necessary to consider KS patients at high-risk of developing MS and T2D throughout their life.

In KS patients with MS or prediabetes, a Diabetes Prevention Program (DPP) should be considered. DPP, consistent in lifestyle changes such as nutritional suggestions (e.g. reducing caloric intake and increasing consumption of food high in monounsaturated fats), and physical activity (exercise prescriptions designed to prevent diabetes are based on aerobic activity and may include resistance training) has provided the strongest evidence for diabetes prevention in the general population [75,76]. Moreover, the use of metformin was effective in reducing the risk of diabetes by one third in individuals at high-risk for the disease [76]. Although solid data regarding

patients with KS are lacking, the use of metformin in these patients might be equally effective.

When a diagnosis of T2D has been made, lifestyle management exerts a pivotal role in diabetes care with the latest guidelines including diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), physical activity intensification, smoking cessation counseling, and psychosocial care [77]. In particular, considering the associated neuropsychological and behavior disorders described in KS, the multidisciplinary management of this aspect is an important factor that needs to be considered in the management of T2D in KS. Considering the well-known cardiovascular alterations [18,28], before starting physical activity a cardiovascular assessment is required, as elsewhere described [18].

No solid evidence is available for which drug is most appropriate for the treatment of diabetes or its complications in KS patients. However, given the fact that fat accumulation and distribution seems to plays a pivotal role in triggering metabolic abnormalities, drugs targeting body fat should be preferred. Although few data are available on the effect of hypoglycemic agents in KS, some drugs appear to be preferential [42,62]. In particular, metformin and GLP-1 receptor agonists should be the preferred drugs to use in KS patients with diabetes. Finally, the few data available suggest that KS patients with diabetes are not easily controlled by insulin treatment [56], therefore prevention strategies should be aggressive to delay the use of insulin. Future research should directly address the issue to provide evidence regarding the best approach for patients with KS and diabetes.

Conclusions

KS is described by a vicious circle and network of complex interactions that establish health complications of patients (Figure 1). Chromosomal abnormalities, influence body composition, causing an increase in body fat (especially intra-abdominal fat), the onset of IR and a related deterioration of carbohydrate metabolism leading to diabetes, but also induce the reduction of androgen secretion. Furthermore, IR aggravates hypogonadism [33] via a direct effect to further

exaggerate the dysfunction of testosterone production by the Leydig cell [78]. In KS, TRT does not appear to change the prevalence of MS or to improve indices of IR, suggesting that more complex and unclear mechanisms sustain the link between KS and MS [40]. An early diagnosis and tailored intervention strategy seem mandatory in patients with KS, and should be aimed at targeting excessive visceral fat deposition.

Compliance with ethical standards

Conflict of interest: Dr. Salzano receives research grant support from Cardiopath. The remaining author declares that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Table I. Studies evaluating metabolic syndrome and insulin resistance in Klinefelter syndrome

Author, year (ref)	*Pts*	*Criteria used for diagnosis of IR or MS*	*Findings*	*Relationship with T*
A. Adult population				
A1.Insulin resistance				
Pei D, 1998 [27]	7	the total area under the curve (AUC) and the incremental AUC of serum insulin concentrations in response to a 75-g oral glucose load, and the insulin suppression test	decreased insulin sensitivity and elevated fasting insulin in KS	Plasma glucose inversely related to T levels
Yesilova Z, 2005 [26]	13	hyperinsulinemic euglycemic clamp	IR prevalence: 39%	T as an independent determinant of whole-body glucose disposal rate with hyperinsulinemic euglycemic clamp
Bardsley MZ, 2011 [37]	89	HOMA	IR prevalence: 24% HOMA > 2.5 9.3% had fasting insulin levels >20 IU/mL	-
A2. Metabolic Syndrome				
Bojesen A, 2006 [24]	70	NCEP/ATP III criteria (all criteria for MS diagnosis were present except for BP)	MS prevalence: 47% in KS (46% in untreated KS vs 49% in treated KS) vs 10% in controls	T therapy did not affect IR (IM T injections [20 pts], oral T undecanoate [14 pts], and mesterolon [1 pt])
Ishikawa T, 2008 [25]	60	revised NCEP/ATP III criteria in Japan (all criteria for MS diagnosis were present except for BP and FBG).	MS prevalence 34% in KS vs. 22% in controls	-
Jiang-Feng M, 2012 [62]	39	IDF criteria	MS prevalence: 30.8% before T treatment, 38.5% after T treatment for a median duration of 4 years in KS vs 15% and 20% respectively before and after T therapy in controls	body weight and BMI significantly increased during long-term T replacement Treatment (before 1993, 100 mg compound T was injected IM at an interval of 10 days; after 1993, 250 mg T undecanoate was injected IM monthly)
Pasquali D, 2013 [28]	69	NCEP/ATP III criteria (18 KS pts had increased waist circumference, 16 had impaired fasting glucose, 3 had diabetes mellitus, 12 had elevated triglycerides, 13 had decreased HDL cholesterol, and 4 had high diastolic blood pressure)	MS prevalence: 49% in KS (47% untreated vs 50% treated) vs 10% in controls	No effect of T therapy (1000 mg long-lasting IM T every 3 months)
B.Pediatric population				

Bardsley MZ, 2011 [37]	89	adaptation of NCEP/ATP III for pediatric use 65% of KS pts had decreased HDL levels, 15% had elevated TG levels, and 49% had a WC >75 percentile. None had elevated BP or FBG.	36% with ≥ 1 MS feature 8% with ≥ 3 MS feature	-
Davis S, 2016 [38]	93 pre-puber tal	adaptation of NCEP/ATP III for pediatric use	80% with ≥1 MS feature 11% with ≥3 MS features	No relationship between T and MS
Davis S, 2017 [39]	93 pre-puber tal	adaptation of NCEP/ATP III for pediatric use	80% with ≥1 MS feature 11% with ≥3 MS features	T therapy had a modest improvement on features of MS and body composition, more expressed in the subgroup of patients who remained prepubertal throughout the study despite a decline in HDL and little bone age advancement. (Oral oxandrolone (Ox) 0.06 mg/kg/die or placebo)

T: Testosterone; MS: metabolic syndrome; KS: Klinefelter Syndrome; IR: Insulin-Resistance; HOMA: homeostatic model assessment: BP; blood pressure, FBG, fasting blood glucose; WC, waist circumference; Pts: patients; IM: intramuscular. National Cholesterol Education Program - Adult Treatment Panel III (NCEP- ATP III) criteria [20]: 1) increased waist circumference (i.e. in Caucasian males >102 cm, in Japan males >85 cm females >88cm); 2) high plasma triglycerides (>150 mg/dl; 3) low HDL-cholesterol (<40 in men and <50 mg/dl in women); 4) elevated systolic or diastolic blood pressure (>135 or 85 mmHg, respectively); 5) impaired fasting glucose (>110 mg/dl). 3 or more of the criteria needed. International Diabetes Federation (IDF) criteria [22]: central obesity with waist circumference >90 cm, plus any two of four additional factors include triglyceride >150mg/dL, highdensity lipoprotein (HDL)-cholesterol < 40 mg/dL (or treatment for dyslipidemia), systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm Hg (or treatment of previous hypertension), and fasting plasma glucose > 100 mg/dL (or previously diagnosed type 2 diabetes). Adaptation of NCEP/ATP III for pediatric use [23]: 1) central obesity with waist circumference >75th percentile for age and gender, 2) high plasma triglycerides (>97 mg/dl; 3) low HDL-cholesterol (< 50 mg/dL, boys aged 15–19 years < 45); 4) elevated systolic or diastolic blood pressure (>90th percentile for age, gender, and height); 5) impaired fasting glucose (>110 mg/dl).

Table II. Diabetes Mellitus in Klinefelter Syndrome

Author, year (ref)	*Patients*	*T2D Prevalence*	*Effect of T replacement therapy (type of T therapy)*
Forbes AP, 1963 **[61]**	41	15%	-
Nielsen J, 1966 **[60]**	25	32%	
Jackson IM, 1966 **[58]**	8	12%	-
Becker KL, 1966 **[59]**	50	10%	-
Zuppinger K, 1967 **[63]**	24	25%	
Nielsen J, 1969 **[56]**	31	39%: specifically 20.8% in patients with 47,XXY karyotype, 100% with other karyotypes (4 patients with 46,XY/47,XXY chimera and 3 patients with 49,XXXXY)	-
Sagara MN, 1986 **[64]**	-	3,9%	-
Takeushi Y, 1999 **[53]**	Rev	15%-50% in Western countries 3.9%-4.1% in Japan	-
Ota K, 2002 **[65]**	895	6.5%	No effect (type of T treatment not reported)
Lichiardopol C, 2004 [66]	31	16% of KS have Prediabetes 0% have T2D	-
Bojesen A, 2004 [14]	781	HR: T1D 2.21: T2D 3.71. Mortality for DM 1.64	-
Swerdlow AJ, 2005 [15]	4806	T2D cause-specific MR: 7.07; SMR:5.8; HR: 1,6	-
Bojesen, A 2006 [24]	70	10% (9% in untreated KS vs 11% in treated KS)	No effect (intramuscular T injections [20 pts], oral testosterone undecanoate [14 pts], and mesterolon [1 pt])
Jiang-Feng M, 2012 **[62]**	39	20.5%; specifically 12.5% in 47,XXY and 57.1% in pts with other atypical karyotypes (46XY/47XXY chimera and others).	Body weight and BMI significantly increased during long-term TRT (before 1993, 100 mg compound T was injected IM at an interval of 10 days; after 1993, 250 mg T undecanoate was injected IM monthly)
Pasquali D, 2013 [28]	69	8% (9% in untreated KS and 6% in treated KS)	No effect (1000 mg long-lasting intramuscular T every 3 months)
Han SJ, 2016 [43]	376	Prediabetes: 26%; specifically, 19.8% in non-obese pts and 38% in obese patients (p <.05) T2D: 12.8%; specifically, 11.6% in non-obese pts and 14.3% in obese pts	-

Rev: review; T: Testosterone; T2D: type 2 Diabetes Mellitus; KS: Klinefelter Syndrome; T1D: type 1

Diabetes Mellitus; MR: mortality ratio; SMR: standard mortality ratio; HR: Hazard Ratio: pts: patients

Figure legends.

Fig1. Vicious circle and network of complex interactions in Klinefelter syndrome.
Klinefelter Syndrome induces hypogonadism and influences body composition, causing an increase in body fat (especially intra-abdominal fat), inducing IR which, in turn, aggravates the hypogonadism via a direct effect on Leydig cell production of residual testosterone. However, testosterone therapy does not appear to change the prevalence of MS or T2D nor improve indices of IR. The mechanisms active in the general population (panel A) or in the patients with KS (panel B) are depicted. Green circles represent the general population. Blue circles represent KS patients. Green or blue arrows indicate mechanisms active in the general population or in KS patients, respectively. The arrows are in continuous or dashed format to indicate an action toward an increase or a decrease of the target parameter, respectively.

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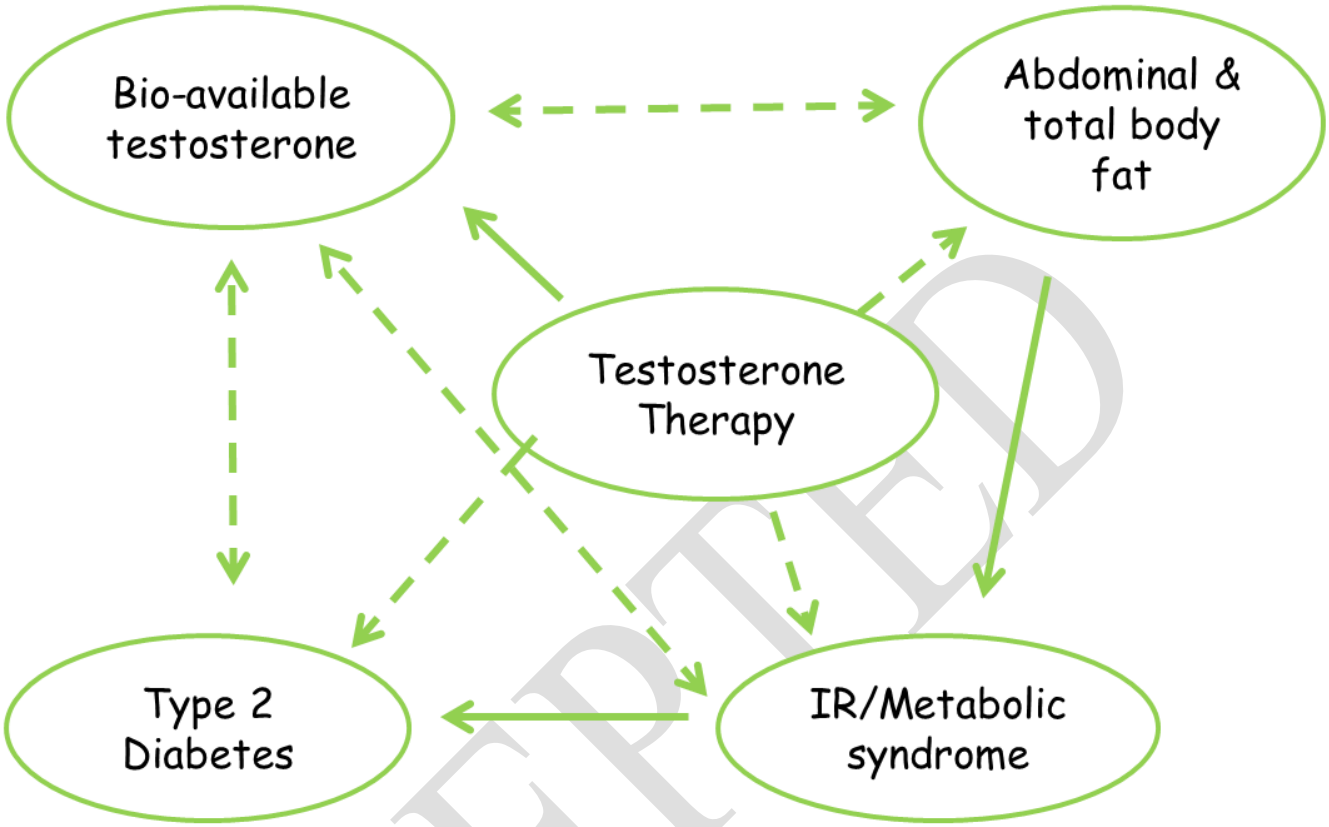
A. General population



B. Klinefelter syndrome patients