



## Why, When and How We Propose Withdrawal Insulin Treatment in Type 2 Insulin Resistant Diabetes

Andreu Nubiola<sup>1\*</sup>, Imma Remolins<sup>2</sup> and Miquel Nubiola<sup>3</sup>

<sup>1</sup>Unitat d'Endocrinologia, Hospital Universitari de L'Esperit Sant. Sta. Coloma de Gramenet, Barcelona, Spain

<sup>2</sup>Unitat de Nutricio, PAMEM (IMAS), Barcelona, Spain

<sup>3</sup>Universitat Ramon Llull, Blanquerna, Nutricio, Barcelona, Spain

\*Corresponding author: Andreu Nubiola, Unitat d'Endocrinologia, Hospital Universitari de L'Esperit Sant. Sta. Coloma de Gramenet, P<sup>o</sup> Garcia Faria 81, 8-3<sup>a</sup>. 08019 Barcelona, Spain, Tel: 607468987, E-mail: [anubiola@hes.scs.es](mailto:anubiola@hes.scs.es)

### Abstract

Insulin treatment is the choice in insulinopenic diabetic patients, in order to prevent or delay microvascular lesions, related to hyperglycaemia. However in insulin resistant type 2 diabetes, the improvement in glycaemic control with insulin, is not without side effects, especially weight gain and hypoglycaemia. Many retrospective or case-control studies of insulin treatment have reported a higher prevalence of CVD in insulin-treated patients. However, many of these patients started insulin therapy in relation to different clinical settings, following this treatment for years. In clinical practice, the physician needs a protocol to assess the possible withdrawal of insulin in some of them.

**Keywords:** Diet, Cardiovascular risk, Hyperinsulinaemia, Obesity, Diabetes, Insulin

### Introduction

Type 2 diabetes (T2DM) is a chronic and progressive process consists of a group of diseases that are characterized by increased plasma glucose concentration as a result of both, changes in the function of the beta and alpha islet pancreatic cells, and different degrees of insulin resistance (IR), which usually behave compensatory hyperinsulinaemia (HI) in relation to the degree of IR [1]. In clinical practice the patient phenotyping is essential to choose the most appropriate treatment, in relation to the underlying pathophysiological alteration, so if beta-cell failure is the principal cause, the patient is usually in normal weight or in progressive weight reduction. In these cases, the use of insulin is the choice in order to normalize blood glucose level. However, approximately 80-90% of patients are usually overweight or obese. In these cases, the predominant underlying pathophysiological mechanism was IR/HI.

It is conclusively established that the microvascular complications of diabetes (retinopathy, nephropathy, and neuropathy) are directly related to the severity and duration of hyperglycaemia, as reflected by the HbA1c [2,3]. However, macrovascular complications are the primary cause of mortality, with myocardial infarction (MI) and stroke accounting for 80% of all deaths in T2DM patients [4].

Why consider withdrawal of insulin in insulin resistant, T2DM

The load of cardiovascular risk factors (CVRFs) includes hypertension, dyslipidaemia (reduced HDL-cholesterol, elevated triglycerides, and small dense LDL particles), obesity (especially visceral), physical inactivity, sub-clinical inflammation, and endothelial dysfunction. This cluster, referred to as metabolic or insulin resistance syndrome, consistently predicts atherosclerotic CVD (ATCVD) [5]. Many studies have reported an association between insulin resistance/hyperinsulinaemia and ATCVD in the general population [6-8]. Moreover, in cross-sectional analyses insulin treatment in T2DM patients is consistently associated with the presence of atherosclerotic CVD (ATCVD) even after adjusting for multiple CVRFs [9]. However, in most studies insulin resistance was not measured directly and control for statistical confounding was incomplete. Thus, in a cohort of carefully phenotyped non-diabetic subjects baseline insulin resistance (as measured by the euglycaemic insulin clamp technique) was independently associated with a small increment in the intima-media thickness of the common carotid artery (carotid intima-media thickness, C-IMT) -an antecedent of CVD [10].

In examining the effect of currently approved glucose-lowering drugs on established CVRFs and, where available, on CV mortality and morbidity, two preliminary considerations are important. First, micro and macrovascular T2DM complications often coexist in the same patient but have partially different pathophysiology and risk factors. Also, the dose-response relation of hyperglycaemia to microvascular complications is significantly steeper than to macrovascular disease [11,12]. Secondly, the vast majority of epidemiologic studies and clinical trials is based on major adverse cardiac events (MACE) as the outcome, which includes CV death, non-fatal MI, and non-fatal stroke (sometimes, also unstable angina requiring hospitalization, amputation, and revascularization procedures are included). These outcomes, however, represent the tip of the iceberg of a gamut of manifestations of CVD [13].

Multiple insulin preparations (rapid, intermediate, and long acting) are available and, when used in combination, insulin can

normalize HbA1c in virtually all T2DM patients. However, the improvement in glycaemic control is not without side effects, especially weight gain and hypoglycaemia [14].

Many retrospective or case-control studies of insulin treatment have reported a higher prevalence of CVD in insulin-treated patients [15-20]. The opposite indication from epidemiological studies and randomized controlled trials remains problematic. The biology of insulin's action on the vasculature is ambivalent. In fact, insulin can promote atherogenesis through several mechanisms. From the clinical standpoint, it is reasonable to assume that in T2DM patients, the positive association between the pharmacological use of insulin and ATCVD may be explained by the cross-sectional, retrospective nature of many studies, [21,17] and by a strong indication bias (e.g., insulin is most often used in long-standing, complicated diabetes). Hypoglycaemia also occurred frequently in ORIGIN (42 and 14% of patients in the glargine and standard therapy groups, respectively); severe hypoglycaemia was associated with a greater risk for all-cause mortality, CV death, and arrhythmic death [22]. Finally, the possibility that high doses of insulin (> 80-100 units/day) in insulin resistant T2DM patients may accelerate the progression of vascular damage cannot be conclusively ruled out [23]. Hyperglycaemia/insulin resistance control should take place within a comprehensive approach in order to reduce cardiovascular risk. Because T2DM is associated with a markedly increased incidence of cardiovascular complications, it is advantageous that the medications used to restore normoglycaemia not aggravate known cardiovascular risk factors (CVRFs), not accelerate the underlying atherogenic process and, optimally, reduce cardiovascular risk.

However, many of these patients started insulin therapy in relation to different clinical settings, when the patient is unable to make changes in your lifestyle or related to glucocorticoid therapy, or after hospitalization, surgery, among others, following this treatment for years. In clinical practice, the physician needs a protocol to assess the possible withdrawal of insulin in some of them. On the other hand, there are numerous studies linking HI with cancer risk [24-30]. Other reasons for the possible withdrawal of insulin are evident in table 1.

When you consider withdrawal of insulin in insulin resistant, T2DM

T2DM, obese insulin treated patients, with the characteristics described above, without clinical insulinopenia criteria when start this treatment (weight reduction), with a correct C - peptide reserve. (C-peptide levels in the morning after having insulin dose by night, can help us) [31].

How consider withdrawal of insulin in insulin resistant, T2DM

Bibliographic data related to a protocol for a possible withdrawal of insulin are surprisingly rare if we consider the frequency of these patients in our clinical practice.

The references we could find back to more than twenty years ago [32-36]. Some studies in bariatric surgery and T2DM, a vague reference to the fact that in some cases, insulin treatment is suppressed after surgery is done, but no protocol specified how. No data are found in this regard, positioning, consensus of the different scientific diabetes societies recommendations. For this reason, it is difficult to choose criteria of evidence-based medicine, so we propose a protocol developed based on logic and experience care, often low considered, to shed some light on this issue (Table 2).

**Table 1:** Other reasons for withdrawal insulin treatment.

1.	Avoid or reduce hypoglycaemia
2.	Provide a more simple treatment
3.	Psychological reasons/Quality of life
4.	Avoid or reduce risk of some type of cancer?
5.	Avoid or reduce hypoglycaemia
6.	Saving Diabetes Education Injection Device Self control

**Table 2:** Protocol for possible withdrawal of insulin treatment.

1.	It is imperative to agree with the patient lifestyle changes
2.	Metformin increasing doses, up to the maximum tolerated dose
3.	Remove your insulin regimen
4.	Start long acting insulin, 0.5u/kg at bed time
5.	If the requirement was < 0.2u/Kg, we can stop insulin immediately.
6.	Consider arGLP1 or isGLT2
7.	Self-monitoring blood glucose each day in the morning, fasting
8.	If three consecutive controls > 150 mg/dl: + 2u. (long acting insulin dose)
9.	If three consecutive controls < 120 mg/dl: - 2u. (long acting insulin dose)
10.	If daily requirement < 0.2u / kg, maintain metformin and remove insulin.
11.	Nutrition educator control every week, for the first month
12.	BMI > 35 and inadequate HbA1c, value consider arGLP- 1 / isGLT2 )
13.	Subsequently, routine monitoring follow

## Conclusion

In different clinical situations, we started insulin therapy in obese patients with T2DM. However, in many cases we can rethink the need to continue this treatment when the patient's condition has changed. However, most clinical guidelines is not explained how. The manuscript is intended to bring some light on this subject.

Just as premature started insulin treatment in T2DM patients with clinical and metabolic criteria of insulinopenia, in order to prevent or delay microvascular lesions related to hyperglycemia, it should also arise in some cases possible removal of insulin treatment in diabetic insulin resistant patients, in order to prevent or delay cardiovascular risk, minimizing hypoglycaemia and excessive weight gain.

It's not intention of the authors indiscriminately removing insulin to patients with T2DM. We provide a protocol to help clinician to try it in patients with features described, since virtually no literature on it. We hope thereby sensitize the various scientific societies in the field of diabetes to develop a protocol agreed in this regard.

## References

1. Reaven GM (1988) Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37: 1595-1607.
2. (1995) UK prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes* 44: 1249-1258.
3. (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352: 837-853.
4. Morrish NJ, Wang SL, Stevens LK, Fulloer JH, Keen H (2001) Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. *Diabetologia* 44: S14-S21.
5. Noto D, Barbagallo CM, Cefalu AB, Falletta A, Sapienza M, et al. (2008) The metabolic syndrome predicts cardiovascular events in subjects with normal fasting glucose: results of a 15 years follow-up in a Mediterranean population. *Atherosclerosis* 197: 147-153.
6. Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, et al. (2001) Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24: 683-689.
7. Hanley AJ, Williams K, Stern MP, Haffner SM (2002) Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. *Diabetes Care* 25: 1177-1184.
8. Pyorala K, Uusitupa M, Laakso M, Siitonen O, Niskanen L, et al. (1987) Macrovascular complications in relation to hyperinsulinaemia in non-insulin-dependent diabetes mellitus. *Diabete Metab* 13: 345-349.
9. Solini A, Penno G, Bonora E, Fondelli C, Orsi E, et al. (2013) Age, renal dysfunction, cardiovascular disease, and antihyperglycemic treatment in type 2 diabetes mellitus: findings from the Renal Insufficiency and Cardiovascular Events Italian Multicenter Study. *J Am Geriatr Soc* 61: 1253-1261.
10. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, et al. (2008) Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med* 168: 1333-1339.
11. Nakagami T1, Kawahara R, Hori S, Omori Y (1997) Glycemic control and prevention of retinopathy in Japanese NIDDM patients. A 10-year follow-up study. *Diabetes Care* 20: 621-622.

12. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, et al. (1995) Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28: 103-117.
13. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296-1305.
14. Henry RR, Gumbiner B, Ditzler T, Wallace P, Lyon R, et al. (1993) Glauber HS. Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-mo outpatient trial. *Diabetes Care* 16: 21-31.
15. Holden SE, Currie CJ (2014) Mortality risk with sulphonylureas compared to metformin. *Diabetes Obes Metab* 16: 885-890.
16. Gamble JM, Simpson SH, Eurich DT, Majumdar SR, Johnson JA (2010) Insulin use and increased risk of mortality in type 2 diabetes: a cohort study. *Diabetes Obes Metab* 12: 47-53.
17. Currie CJ, Poole CD, Evans M, Peters JR, Morgan CL (2013) Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. *J Clin Endocrinol Metab* 98: 668-677.
18. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, et al. (2010) Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. *The Lancet* 375: 481-489.
19. Colayco DC, Niu F, McCombs JS, Cheetham TC (2011) A1C and cardiovascular outcomes in type 2 diabetes: a nested case-control study. *Diabetes Care* 34: 77-83.
20. Eurich DT, Simpson S, Senthilselvan A, Asche CV, Sandhu-Minhas JK, et al. (2013) Comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes: retrospective population based cohort study. *BMJ* 346: f2267.
21. Gamble JM, Simpson SH, Eurich DT, Majumdar SR, Johnson JA (2010) Insulin use and increased risk of mortality in type 2 diabetes: a cohort study. *Diabetes Obes Metab* 12: 47-53.
22. ORIGIN Trial Investigators Mellbin LG, Ryden L, Riddle MC, Probstfield J, Rosenstock J, et al. (2013) Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. *Eur Heart J* 34: 3137-3144.
23. Rensing KL, Reuwer AQ, Arsenault BJ, von der Thusen JH, Hoekstra JB, et al. (2011) Reducing cardiovascular disease risk in patients with type 2 diabetes and concomitant macrovascular disease: can insulin be too much of a good thing? *Diabetes Obes Metab* 13: 1073-1087.
24. Nubiola A, Ferrer M, Remolins I (2015) The association of hyperinsulinemia with cardiovascular risk and cancer poses new challenges in the treatment of the insulin resistance type 2 diabetes patient. *Hipertens Riesgo Vasc* 32: 21-26.
25. Lakka HM, Lakka TA, Tuomilehto J, Sivenius J, Salonen JT (2000) Hyperinsulinemia and the risk of cardiovascular death and acute coronary and cerebrovascular events in men. The Kuopio ischaemic heart disease risk factor study. *Arch Intern Med* 160: 1160-68.
26. Rubins HB, Robins SJ, Collins D, Nelson D, Elam MB, et al. (2002) Diabetes, plasma insulin and cardiovascular disease subgroup analysis from the department of veterans affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med* 162: 2597-2604.
27. Arcidiacono B, Iiritano S, Nocera A, Possidente K, Nevoletta MT, et al. (2012) Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. *Exp Diabetes Res* 2012: 789174.
28. Braun S, Bitton-Worms K, LeRoith D (2011) The link between the metabolic syndrome and cancer. *Int J Biol Sci* 7: 1003-1015.
29. Jaggars JR, Sui X, Hooker SP, LaMonte MJ, Matthews CE, et al. (2009) Metabolic syndrome and risk of cancer mortality in men. *Eur J Cancer* 45: 1831-1838.
30. Belfiore A, Malaguarnera R (2011) Insulin receptor and cancer. *Endocr Relat Cancer* 18: R125-147.
31. Kumar D, Luna-Lollie T, Mahda S (2001) One-hour meal tolerance test to assess withdrawal of insulin therapy in overweight patients with type 2 diabetes. *Endocr Pract* 7: 256-61.
32. Kromann H, Borch E, Gale EA (1981) Unnecessary insulin treatment for diabetes. *Br Med J (Clin Res Ed)* 283: 1386-1388.
33. Bulger K, McKenna TJ (1986) Improvement in diabetic control on complete withdrawal of inappropriately prescribed insulin 155: 392-393.
34. Cohen M, Crosbie C, Cusworth L, Zimmet P (1984) Insulin—not always a life sentence: withdrawal of insulin therapy in non-insulin dependent diabetes. *Diabetes Res* 1: 31-34.
35. Armitage M, Frier BM, Duncan LJ (1983) A misplaced medal? 50 years of unnecessary insulin treatment. *Br Med J (Clin Res Ed)* 286: 844.
36. Bennett S, Stewart M (1998) Withdrawal of insulin therapy after adjunctive treatment with acarbose in a patient with Type 2 diabetes mellitus. *Practical Diabetes International* 15: 123-124.