

Supplemental material

**Protocol for the Individualized multifactorial treatment of new clinically diagnosed type 2 diabetes in general practice (IDA)**

**- A prospective controlled multicenter open-label intervention study**

**Motivation for the proposed glucose-lowering treatment of specific pathophysiological phenotypes**

Ideally, treatment should target the pathophysiological abnormalities. As patients with insulinopenic T2D have beta cell failure, basal insulin and meal-time insulin are recommended. Beta cell failure has been linked to poor response to GLP-analogs[1]. Patients with classical and hyperinsulinemic T2D have high or very high insulin resistance and appear to have increased cardiovascular morbidity at diagnosis[2] compared to patients with insulinopenic T2D with low insulin resistance. The primary focus in these two groups is thus to target insulin resistance. As hyperinsulinemic patients have severe insulin resistance, glitazones are also recommended for this group. Insulin is introduced earlier in the algorithm for classical T2D, as patients in this group also exhibit a degree of beta cell insufficiency. Metformin[3], GLP-1 analogs[4-6], glitazones[7] and SGLT2-inhibitors[8 9] are known to decrease insulin resistance. GLP-1 analogues also increase insulin secretion, restore first- and second-phase insulin response, and reduce glucagon secretion and body weight. A meta-analysis of randomized trials of pioglitazone reported a reduced incidence of death, myocardial infarction, and stroke compared to other medications[10 11]. This finding is supported by favorable effects on cardiovascular surrogate markers[7]. However, the incidence of heart failure was increased by pioglitazone treatment[10 11], and pioglitazone also increase the risk of fractures in women[12]. Pioglitazone has been linked to bladder cancer[13], but a recent multipopulation analysis, focusing on statistical procedures minimizing allocation bias found no such association[14]. In addition

recent long-term study, including a case-control design, was not able to link bladder cancer to use of pioglitazone[15]. GLP-1 analogs are chosen over dipeptidyl peptidase-4 (DDP-4) inhibitors as GLP-1 analogs reduce weight and cardiovascular disease and mortality[16], while DDP-4 inhibitors have no proven effect on weight or macro- and microvascular complications[17]. An increased risk of heart failure might also be present[17 18]. Moreover DDP-4 inhibitors do not seem to reduce insulin resistance[19]. For these reasons we only recommend DDP-4 inhibitors in patients who do not want to use GLP-1 analogs. In case insulin becomes relevant we recommend the DDP-4 inhibitor to be discontinued in order to reduce medication which has no proven effect on clinical endpoints. In patients of Asian inheritance incretin-based therapy has been shown to be more effective and is therefore first-line treatment in Asia[20]. Evidence is accumulating that SGLT-2 inhibitors decrease the risk of major adverse cardiovascular events, cardiovascular death, heart failure, and death from any cause [21-23]. SGLT-2 inhibitors also induce weight reduction. The primary population, in the dominating studies, has been patients with prior cardiovascular disease and therefore we only recommend SGLT-2 inhibitors in this subpopulation. Sodium retention is decreased by GLP-1 analogs and SGLT-2 inhibitors, and increased by pioglitazone. The rationale for introducing pioglitazone after GLP-1 analogs and SGLT-2 inhibitors is to minimize pioglitazone-induced sodium and fluid retention, thereby preventing heart failure in susceptible patients. Bariatric surgery has been shown to reduce mortality, cardiovascular morbidity, and cancer incidence compared to usual care [24-26], and analyses restricted to diabetic patients have had the same results [27]. Diabetes remission rates also remained high after 10 years [24]. The Swedish Obese Subjects (SOS) study found that fasting insulin levels predicted a successful surgical outcome, in terms of mortality and CVD [24]. This supports bariatric surgery as a recommendation for patients with hyperinsulinemic T2D.

The degree of evidence varies for managing specific forms of diabetes. As patients with secondary diabetes have a primary beta cell defect, basal and meal-time insulin are recommended [28]. Patients with latent autoimmune diabetes of the adult (LADA) have diabetes-related antibodies, as seen in type 1 diabetes, but initially present as a T2D phenotype. Over time patients with LADA develop beta cell insufficiency, and

therefore basal and meal-time insulin are recommended. A review concluded that insulin therapy preserves beta cell function better than sulphonylureas, although relevant studies on treatment of LADA are scarce [29]. Since many patients with LADA have a type 2 diabetes phenotype with adipositas, metformin is also recommended if BMI>25kg/m<sup>2</sup>. Maturity-onset diabetes of the young (MODY) encompasses several monogenetic forms of diabetes. Patients with MODY3 and MODY1 have insulin secretion defects that respond to sulphonylureas[30 31]. Patients with MODY2 have a mutation in the glucokinase gene, which alters the set point of glucose control, while glucose regulation is intact [32 33]. Patients with MODY 2 rarely develop complications and the preferred intervention is diet.

Administration of glucocorticosteroids has the potential to induce diabetes onset and to exacerbate existing type 2 diabetes. It has been reported that prednisolone in particular enhances postprandial plasma glucose values in patients without known diabetes, with unchanged glucose levels at night and in the morning [34-36]. The same results have been reported for patients with type 2 diabetes, impaired glucose tolerance and normal glucose tolerance,[37-39]. Glucocorticoids impair both IS and BCF [40]. Evidence for optimal treatment of steroid-induced diabetes is sparse and based on case reports. Accordingly, there is little consensus regarding treatment. Insulin isophane (NPH) has been advocated [41], as well as prandial insulin [40]. In patients with metabolic syndrome or T2D, it has been found that sitagliptin did not improve GC-induced postprandial glucose excursions. [42 43]. Nateglinid [35 39] and glitazones have shown some benefit [44 45] and metformin has been found to improve postprandial glucose values from well above 11 to below 7.5 mmol/l in one patient[43]. Intravenous administration of exenatide has been observed to improve postprandial glucose values [46], but only when administered at breakfast and lunch [47]. In cases treated with exenatide, addition of SU was needed to achieve glycemic control. A comparative study of NPH insulin and insulin glargine with bolus insulin found that glucose control could be achieved, with no differences between agents [48].

### **Motivation for the proposed individual lifestyle intervention**

Web- and smartphone-based applications are a possible means for effective and time-saving patient counseling. However, they can result in low compliance over time and thus may be unfeasible as stand-alone lifestyle interventions. A Danish internet platform called Liva has been developed during the past decade by a team of dietitians, computer programmers, and physicians as a commercial weight management program. Its guiding principle is to improve the cost-effectiveness of established best practice for dietician-supported weight management by using an Internet platform to facilitate interactive communication between dietitians and users, as well as by peer-to-peer support through the online community. The program was developed iteratively through trial and error from an initial prototype and is now a well-established commercial product used by 10,000 predominantly healthy overweight or moderately obese persons. The effect of online dietician counseling based on this system was examined in a prospective non-controlled pilot study in obese subjects, and an average weight loss of 7.0 kg (95% CI: 4.6 to 9.3 kg) was observed after 20 months,[49].

In Denmark, diet recommendations for the general population and for patients with T2D are 45%-60E% carbohydrates, 10%-20E% proteins, and 25%-40E% fat[50]. It is being debated whether a diet with reduced carbohydrates (40E% fat, 40E% carbohydrates, and 20E% proteins) and an increased amount of unsaturated fat favors glycemic control in patients with T2D compared to current recommendations [51 52]. Several studies support the beneficial effects of the reduced carbohydrate diet on glycemic control for patients with T2D [53].

Poor physical fitness is one of the most important independent predictors of disease progression, morbidity, and mortality for patients with T2D [54 55]. It has been found that supervised exercise increases fitness,[56]. With the increasing prevalence and incidence of T2D, fully supervised training programs for all T2D patients would be very costly and thus unrealistic. We recently tested the feasibility of implementing unsupervised interval walking training (IWT), compared with continuous walking training, among patients with T2D in a four-month randomized controlled trial [57]. We found that IWT, but not continuous walking,

had remarkably beneficial effects on physical fitness level and glycemic control. Moreover, this was achieved with a compliance rate of ~90% [57] and high long-term adherence [58]. We later tested the unsupervised IWT modality for 17 months in a setting with a compliance rate of >60%[59]. On this basis, we believe that the IWT exercise modality can be implemented as unsupervised exercise in a real-life setting. To permit large-scale implementation, guide correct training intensity, and improve feasibility for patients, we developed a smartphone application (InterWalk) that can be downloaded free of charge from App Store.

### **Motivation for the proposed lipid-lowering treatment**

Statin treatment reduce cardiovascular disease and mortality in type 2 diabetes, with no difference in effect between phenotypes and with no clear lower LDL-C boundary of effect[60]. Intensive statin treatment compared to moderate statin treatment in type 2 diabetes patients with prior cardiovascular disease reduce a combined cardiovascular endpoint[61]. Addition of ezetimibe to statins are not extensively investigated and addition to high dose statin dose is not evaluated[62]. PCSK9 inhibitors do provide additional lowering of LDL-C when added to other lipid lowering medication and might also reduce any CVD[63]. Further studies is needed to establish the effect on cardiovascular disease. The effect in patients with diabetes seem to be equal or better than in patients without diabetes. As the evidence on cardiovascular endpoints for combination of lipid-lowering drugs is low we advocate treatment with statins in monotherapy.

### **Determination of covariate balance in propensity score matching**

The usefulness of the propensity score models can be tested by how well covariates of the intervention and control patients match. The standardized difference should be used to compare covariates:

$$d = \frac{\bar{X}_{intervention} - \bar{X}_{control}}{\sqrt{\frac{S_{intervention}^2 - S_{control}^2}{2}}}$$

$$d = \frac{\hat{p}_{intervention} - \hat{p}_{control}}{\sqrt{\frac{\hat{p}_{intervention}(1 - \hat{p}_{intervention}) + \hat{p}_{control}(1 - \hat{p}_{control})}{2}}}$$

$\bar{x}$  denotes the mean of a continuous covariate.  $S$  is the variance.  $\hat{p}$  denotes the prevalence of dichotomous covariates. With 1:k matching, the weighted mean should be used. If  $n$  control patients are matched per intervention patient, the weight should be  $1/n$ . A difference below 0.1 is considered acceptable and should be achieved for all covariates [64]. The variance ratio should also be estimated as  $VR = \frac{S_{intervention}^2}{S_{control}^2}$ . Ratios between 0.5 and 2.0 are considered acceptable [65]. If the model does not conform to this criterion, a new model with inclusion of interaction terms and/or higher-order terms will be fitted. A quantile-quantile plot (or similar approach) for each variable (interactions can also be evaluated) should be used to compare the distribution in the intervention and control groups [66].

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