Type 2 diabetes mellitus (T2DM) is a chronic endocrine disorder characterized by insulin resistance in peripheral tissue and a delay or deterioration of insulin secretion, due to gradual deterioration of β-cell function, leading to abnormal high levels of blood glucose. Patients need to maintain glycaemic control (glycaemic control refers to the daily practice of monitoring and managing blood glucose levels in order to them as close to normal as possible) in order to reduce the risk for cardiovascular complications caused by chronic high blood glucose.

The initial treatment of T2DM consists of lifestyle adaptation (more healthy nutrition and more physical activity). Subsequently, when lifestyle adaptation alone is insufficient to maintain glycaemic control, various oral blood-glucose lowering medications are available. When β-cell deterioration further progresses, patients with T2DM require injections with insulin to maintain glycaemic control. Insulin therapy makes patients prone to very low levels of blood-glucose: hypoglycaemia.

With the development of rapid-acting and long-acting insulin analogues, self management of patients has become less strict. However, patients may often feel frustrated, overwhelmed or afraid because of the never-ending daily self-care. Despite these demotivating factors, patients need to maintain glycaemic control in order to reduce the risk for cardiovascular complications. This constant battle with daily self-care may negatively impact the Health-Related Quality of Life (HRQoL) of a patient. HRQoL refers to the impact of health and illness on a person’s evaluation of his or her own life.

Impaired HRQoL negatively impacts self-care, which may lead to poorer treatment outcomes, which in turn increase healthcare utilization as well as the risk for diabetes complications. According to both the American Diabetes Association and the European Association for the Study of Diabetes, care for patients with diabetes should aim at improving treatment outcomes while safeguarding HRQoL. It can even be argued that HRQoL is the single most important outcome for patients with a chronic disorder, since patients have to live with this disorder mostly for the rest of their lives.

The interaction between diabetes and HRQoL is complex, as research to date has shown that several aspects of diabetes may negatively impact a patient’s HRQoL. Among these are diabetes complications and side-effects of insulin therapy, such as dietary restrictions and hypoglycaemia. Nevertheless, current understanding of the interaction between diabetes and HRQoL is limited.

In contemporary diabetes care, psychosocial demands of diabetes are acknowledged, yet interaction with patients is usually limited to medical issues. Little room is available for understanding the patient’s conception of the disease. Enhanced
insight in the patient’s view of insulin therapy, effects of insulin therapy initiation or intensification on a patient’s HRQoL and the association between medical outcomes and HRQoL may contribute to bringing the patient and healthcare provider together in collaborative diabetes care. This increases opportunities for and acceptance of optimally effective clinical interventions, while safeguarding a patient’s HRQoL.

The aim of this thesis was bilateral. Firstly, it was aimed to study the potential impact of long-acting insulin initiation or insulin therapy intensification on three different aspects of HRQoL in adult patients with T2DM who were in suboptimal glycaemic control, accompanied by possible explanations for change in HRQoL following therapy change. Secondly, it was aimed to enhance our understanding of HRQoL in T2DM, namely to enhance our insight into fear of hypoglycaemia in patients with T2DM and to psychometrically assess a commonly used HRQoL measure in patients with T2DM.

In order to attain these research goals, data from four studies were used: SHARED (Survey of Health care professionals and patients to Assess Real perceptions of Diabetes issues), SPIRIT (Study of the Psychological Impact in Real care of Initiating insulin glargine Treatment), ESPRIT (Effect Study on Patient-Reported outcomes in Insulin glargine Treatment) and a depression screening study. The findings from these studies will be discussed in the following paragraphs corresponding with the chapters of the thesis.

In Chapter 2, the scope and underpinnings of Psychological Insulin Resistance (PIR) across western nations was studied using data from the SHARED study. The SHARED study was a cross-sectional multinational survey, in which diabetes patients, nurses, general practitioners and diabetes specialists were invited to participate. The survey contained questions about perceptions towards various aspects of diabetes and its therapy, including the use of insulin. Insulin-naïve Patients with T2DM were asked how willing they would be to initiate insulin therapy if it would be recommended by their physician. Positive and negative beliefs about insulin and oral medications were asked, as well as diabetes distress. PIR was found to be common: 35% of the patients expressed ambivalence and 17% expressed reluctance to initiate insulin if it would be recommended by their physician. Both ambivalence and reluctance to initiate insulin were associated with elevated levels of diabetes distress and an elevated number of negative beliefs about current (oral) medications. A considerable proportion of patients with T2DM were
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ambivalent or unwilling to initiate insulin. These findings are indicative that PIR may reflect a broader discomfort with medication, diabetes or healthcare in general.

Consequently, in Chapter 3, the impact of initiation of long-acting insulin glargine on HRQoL was studied in insulin-naïve, suboptimally controlled (HbA1c >7%; 53 mmol/mol) patients with T2DM using data from the SPIRIT study. The SPIRIT study was a multicentre longitudinal observational study with a follow-up of 6 months. Patients with T2DM in Dutch primary care with a clinical need to initiate insulin therapy (N=911) initiated long-acting insulin, in combination with either oral medications, rapid-acting insulin, or both. At insulin initiation, perceptions towards insulin were measured using five items derived from the Insulin Treatment Appraisal Scale, a commonly used instrument to capture perceptions towards insulin. In addition to data on weight, hypoglycaemia and glycaemic control, data on three aspects of HRQoL were collected at, and 3 and 6 months after insulin initiation: the Worry subscale of the Hypoglycaemia Fear Survey was used to measure fear of hypoglycaemia, the Diabetes Symptom Checklist Revised was used to measure diabetes symptom distress and the World Health Organization five well-being index was used to measure emotional well-being. One quarter of the patients (26%) appeared to have negative perceptions towards insulin at insulin initiation. Three months after initiation of long-acting insulin, a moderate (Cohen’s d 0.39, p<0.001) increase in emotional well-being was observed, despite slight weight gain and along with a 1% mean decrease in HbA1c. Furthermore, small to moderate decreases (Cohen’s d -0.14 and -0.34, p<0.002) in fear of hypoglycaemia and diabetes symptom distress were observed. These observations were sustained six months after insulin initiation. At this follow-up point, a slight decrease in the proportion of patients who had experienced ≥1 symptomatic, nocturnal or severe hypoglycaemic episode was observed. Initiation of long-acting insulin in suboptimally controlled patients with T2DM does not negatively impact fear of hypoglycaemia and diabetes symptom distress and has a small to moderate positive impact on emotional well-being.

Chapter 4 was aimed to test whether improvement in HbA1c following insulin treatment intensification was associated with improvements in HRQoL in patients with T2DM who were in suboptimal glycaemic control and used either NPH insulin, premixed insulin or insulin detemir using data from the ESPRIT study. The ESPRIT study had the same design as the SPIRIT study and the same variables at baseline, 3 and 6 months were measured, but included T2DM patients who were in suboptimal glycaemic control while using NPH insulin, premixed insulin or insulin detemir. Patients initiated insulin glargine at baseline and were followed for 6 months. Similar data as in the SPIRIT study were collected. Insulin therapy was intensified for these patients. After therapy
intensification, improvements in HRQoL were observed: an increase in emotional well-being was observed, along with a decrease in diabetes symptom distress (Cohen’s d 0.27 and 0.39 respectively, p<0.001 for both). Statistically significant, yet very weak longitudinal associations between glycaemic control (HbA1c) and emotional wellbeing and diabetes symptom distress were observed.

In Chapter 5, psychometric and depression screening properties of the WHO-5 were investigated in Dutch outpatients with type 1 (N=384) and type 2 (N=549) diabetes, using data from the depression screening study. The depression screening study was a multicentre randomised controlled trial, aimed to test the effects of screening for depression with subsequent feedback to the patient, his/her internist and primary care physician in adult Dutch patients with type 1 and 2 diabetes in secondary care. In this thesis, baseline data from this study were used to assess psychometric and depression screening properties of a commonly used self-report tool to assess emotional well-being: The WHO-5 wellbeing index. A single factor structure of the instrument was confirmed using confirmatory factor analysis, both for patients with type 1 diabetes (RMSEA=0.094, CFI=0.99) and patients with type 2 diabetes (RMSEA=0.089, CFI=0.99). The instrument has been found to have a high internal consistency (Cronbach’s α 0.91 for patients with type 1 and 0.93 for patients with type 2 diabetes). Moderate to strong concurrent validity has been found with depressive symptom (PHQ-9) scores, diabetes distress (PAID) scores and perceived mental health status (SF-12 MCS score). ROC analyses revealed that a WHO-5 score of <50 had best performance as a first indication for depression against the PHQ-9. The WHO-5 is a psychometrically sound instrument to monitor emotional well-being in both patients with type 1 and patients with type 2 diabetes. The instrument appears to be suitable as a depression screening instrument.

In Chapter 6, potential cut-off scores for clinically meaningful fear of hypoglycaemia on the worry subscale of the Hypoglycaemia Fear Survey (HFS-W) were explored in patients with T2DM using baseline data from both the SPIRIT and ESPRIT studies. Because of the lack of a gold standard for scores indicating elevated fear of hypoglycaemia, three statistical and one content related approach were applied to define a clinically meaningful threshold for elevated fear of hypoglycaemia on the HFS-W: 1) modal score distribution criterion, 2) scores two standard deviations above the mean (standard deviation criterion), 3) concurrent validity with severe hypoglycaemia and suboptimal well-being (concurrent validity criterion), and 4) as a content-related approach, an elevated score (3 or 4) on ≥1 HFS-W item (elevated item endorsement criterion). It was examined which approach had the strongest association with severe hypoglycaemia history and suboptimal well-being (WHO-5<50), which are
both consistently associated with fear of hypoglycaemia. In the modal distribution criterion, it was found that 19% of the patients reported no fear of hypoglycaemia at all (score of 0) on the HFS-W. Using the standard deviation criterion, five percent of the patients reported elevated fear of hypoglycaemia (HFS-W≥50). Following the concurrent validity criterion, patients with severe hypoglycaemia reported significantly higher mean HFS-W score than those who had not (25±20 vs. 15±17, p<0.001). Patients with suboptimal well-being reported higher HFS-W scores than those with satisfactory well-being: 20±18 and 13±15 respectively (p<0.001). Twenty-six percent of the patients had elevated fear of hypoglycaemia defined by the item endorsement criterion (mean HFS-W score 35±19). The item endorsement criterion was most strongly associated with severe hypoglycaemia history and suboptimal well-being. These findings suggest that an elevated score (≥3) on at least one HFS-W item is a viable approach to determine elevated fear of hypoglycaemia in patients with T2DM. More research to corroborate the results in more diverse populations in necessary.

In the following paragraphs, these findings will be briefly discussed. Although patients or healthcare providers may have concerns about insulin initiation, there seems to be no reason related to clinical or patient-reported outcomes to withhold or delay initiation of insulin therapy or insulin therapy intensification. A subgroup of patients will probably need increased psychological attention or more intensified education before or during insulin therapy. These patients may be identified by the multidisciplinary diabetes care team with validated screening tools for psychological problems (e.g. the WHO-5 well-being index), based on an expressed discontent with current medical care or on basis of intuition to provide adequate support or care.

Associations between HbA1c and fear of hypoglycaemia, diabetes symptom distress and emotional wellbeing are weak, which is in line with results from earlier research. This can be due to the fact that HbA1c is a very specific diabetes outcome that is indicative of mean blood glucose over several weeks and is at best weakly related to HRQoL. A chronically elevated or alternatively, (near-)normal HbA1c can be indicative of underlying aspects that negatively impact a patient’s life (e.g. fear of diabetes complications, fear of hypoglycaemia or concerns about one’s health). In this sense, HbA1c can be regarded as a tip of an iceberg for healthcare providers that a patient copes in an inadequate way with his or her diabetes, due to certain beliefs, issues or fears. Because of the above, it is hoped that further research in this area lays more focus in the way patients cope with their diabetes instead.
In the current paradigm of collaborative, patient-centered chronic care, as opposed to prescriptive guidelines, therapy should be tailored to the needs, preferences and tolerances of a patient. In this light, HRQoL related variables should play a more prominent role than they have before. Over the past decades, the repertoire of treatment options for T2DM has increased, extending options for treatment tailoring. Modern therapies, such as GLP-1 receptor agonists and DPP-4 inhibitors might be able to delay insulin therapy in patients with T2DM. These 2 drug classes are associated with a low incidence of hypoglycaemia. However, contemporary insight in the impact of these therapies on HRQoL related variables, including worries related to hypoglycaemia is limited. Eventually, patients with T2DM need to initiate insulin due to the ‘natural’ progression of the disease. With the development of very long acting insulin (1 injection a week), it is probable that risk for hypoglycaemia further decreases. While these developments of newer medications are promising, they do not resolve fears worries related to hypoglycaemia and therapy change. Hypoglycaemia and related worries and fears will remain a problem for as long as an artificial pancreas is unavailable. It is hoped that this thesis stimulates research into the effects of modern therapies on HRQoL related variables such as fear of hypoglycaemia, well-being and concerns related to therapy or therapy intensification in a collaborative care setting.