

Gastrointestinal manifestations in patients with diabetes mellitus

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Valorisation

In a document published by McKinsey in 2013¹, it is stated that by 2040, due to increasing demand and supply of health care, roughly 25% of the Netherlands' gross domestic product will be spent on its healthcare system. In pursuit of a sustainable and high quality health care system, health care managers were interviewed and bundled their thoughts in the following consensus: by 2040 the Netherlands should have the best possible health care system in the world, in term of quality and accessibility, while maintaining a fair balance between costs and returns, but most importantly the health care system emphasizes health and staying healthy. In other words, a health care system that particularly promotes effective preventive measures instead of a narrow emphasis on cure. In general, this thesis focusses on early recognition and diagnosis of gastrointestinal manifestations in patients with diabetes mellitus and provides data supporting a sustainable health care system.

Diabetes mellitus is a global health concern with a high and growing prevalence of about 9% in adults globally. Diabetes mellitus can be viewed as an economic burden with 12% of global health expenditure according to the international diabetes federation². The global cost is predicted to approach 1,452 billion dollar by 2040 due to the increased prevalence of risk factors for diabetes, such as obesity, and the ageing of the world's population. Logically, diabetes mellitus is a chronic disease that needs the attention of health care managers and policymakers. In attempt to reduce diabetes incidence, numbers of trials have emerged and showed that type 2 diabetes mellitus can be prevented or even delayed through lifestyle programs or with timely start of metformin in pre-diabetic individuals³⁻⁵. Unfortunately, up to this date, the ideal cost-effective translation of these programs into 'real-world' settings is not known and remains a major challenge⁶. It is clear, to prevent rising health care costs, diabetes incidence needs to be reduced by means of effective primary prevention strategies. In chapter 3 of this thesis, the intestinal barrier is reviewed in relation to diabetes mellitus development. When current preventive strategies fail or need improvement, inspiration could be derived from new insights. In chapter 3 we conclude that more understanding of the intestinal barrier could have important clinical implications by potentially opening new horizons in the treatment and prevention of diabetes mellitus. For instance, future therapeutic drugs or specific diets that focus on enhancing the intestinal barrier function could be a part in the prevention strategies regarding metabolic diseases such as diabetes mellitus. ●

However, once diabetes mellitus is an established disease, focus must shift towards controlling the disease and preventing costly but also disabling diabetic complications such as vascular diseases, nephropathy and retinopathy. This thesis focusses on the less notorious but equally relevant gastrointestinal manifestations of diabetes mellitus. In chapter 2 of this thesis, we observed a significantly increased prevalence of the gastrointestinal symptoms diarrhea, bloating and early satiety, but also of anxiety and depression in patients with type 2 diabetes mellitus. The importance of viewing gastrointestinal and psychological symptoms simultaneously, as factors that can influence each other in either direction, is emphasized and considered relevant for physicians treating patients with diabetes. Early recognition and treatment initiation of these symptoms is key as studies

show that gastrointestinal complaints impact work productivity and is associated with absenteeism⁷ and effective treatment improves productivity⁸.

The major part of this thesis focusses on the association between diabetes mellitus and colorectal cancer. Colorectal cancer is the third most common cancer in men (~10%) and the second in women (~9%) with a mortality rate of 8.3 per 100,000 person years. In 2011 in the Netherlands, the costs of colorectal cancer care accumulated up to 488 million euro which contributed to ~10% of all cancer related health care costs⁹. Considering these numbers, it may be said that colorectal cancer has major impact on healthcare costs and certainly on the population's health in general. Currently, the colorectal cancer incidence rates are stabilizing and are expected to decrease in countries where population based CRC screening has been implemented.

Studies confirm the effectiveness of screening of the average risk population with colonoscopy and performing polypectomy in preventing colorectal cancer¹⁰. Colorectal cancer screening has recently (2014) been implicated in the Netherlands and the definite yield in terms of colorectal cancer incidence and mortality reduction has yet to be observed by the Dutch cancer registries. Since screening and surveillance programs are costly in terms of money and workforce the cost-effectiveness should be hold in account continually. One way of increasing effectiveness of colorectal screening programs is by screening those individuals at higher risk for colorectal cancer.

In this thesis, a moderate increased prevalence of colorectal adenomas (chapter 6) and incidence of colorectal cancer (chapter 4) in T2DM was observed. In chapter 7 of this thesis, particularly young individuals with type 2 diabetes mellitus appeared at higher colorectal cancer risk compared to their peers without diabetes. In chapter 7, a young diabetic patient was defined by a diagnosis of diabetes before the age of 55 years, the age at which individuals are enrolled in the colorectal cancer screening program. An earlier initiation of CRC screening in individuals with type 2 diabetes mellitus may be cost-effective. In the discussion section of this thesis, based on current colorectal cancer crude incidence rates, as reported by the Netherlands Comprehensive Cancer Organization, a simple calculation showed that the crude incidence of colorectal cancer in men and women with diabetes aged 50 to 54 years is comparable with the colorectal cancer incidence in the general population aged 55 to 59 years. This comparability in CRC incidence suggests that the FIT test, used in the current screening program, could harbor the same diagnostic yield.

Defining a high(er) risk subpopulation to screen is one way of optimizing screening strategies. Another way is to improve the effectiveness of the instruments used in the screening program. For instance, in chapter 6 of this thesis we have documented that individuals with diabetes that underwent a colonoscopy more often had an inadequate bowel preparation as compared to controls without diabetes. Paying attention to risk factors associated with an inadequate bowel preparation in pre-colonoscopy interviews followed by simple adjustments may help to improve adenoma detection and polyp removal¹¹. Moreover, expensive and time-consuming repetitions of colonoscopies may be prevented.

In the future, we may be able to focus even more on the risk of the individual. For instance, personalized risk-based colorectal screening for which questionnaires and biological samples can be used to collect data from large groups of the population. This data can be used to unveil risk factors, their risk factor interactions, and categorize individuals into predefined risk categories (e.g. high risk vs. intermediate vs. low risk).

Epigenetic markers can be used to define a part of the colorectal cancer risk profile. Numerous SNP's have been reported to be associated with increased risk of developing colorectal cancer. It is very plausible that other types of biomarkers, like serum proteins or hormones of interest will be found. In chapter 5 of this thesis we observed an increased colorectal cancer risk in individuals with a genetic variation in the IGF pathway, which was more pronounced in individuals with diabetes mellitus. Studies like the one in chapter 5 could revalue phenotypic risk factors by means of genetic profiling.

In terms of screening, a political trade-off is made between benefits (e.g. life years gained), harms (e.g. colon perforation) and costs. A study has pointed out in micro-simulation models that screening based on risk stratification can particularly reduce harms. As false positives outcomes are consistently lower with this method². On the one hand the costs of defining risk categories in screening can be expected to increase with available biodata. On the other hand, individuals needing diagnostic investigations, such as colonoscopies, are reduced up to ~25% according to one published model³, which in turn could reduce the screening costs.

In summary, we should pursue a sustainable future health care that particularly promotes effective preventive measures instead of adhering to a narrow emphasis on cure. This thesis can add to the knowledge needed for effective early interventions or even prevent the gastrointestinal complications associated with diabetes mellitus.

References

- 1 A vision for Dutch health care in 2040 | McKinsey & Company. Available at: <https://www.mckinsey.com/netherlands/our-insights/a-vision-for-dutch-health-care-in-2040>. (Accessed: 3rd February 2018)
- 2 Diabetes Atlas. International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels, Belgium: International Diabetes Federation, 2015. Available at: <http://www.diabetesatlas.org>. (Accessed: 25th October 2016)
- 3 Knowler, W. C. et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 346, 393-403 (2002).
- 4 Johnson, M. et al. Can diabetes prevention programmes be translated effectively into real-world settings and still deliver improved outcomes? A synthesis of evidence. *Diabet. Med. J. Br. Diabet. Assoc.* 30, 3-15 (2013).
- 5 Hemmingsen, B. et al. Diet, physical activity or both for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk of developing type 2 diabetes mellitus. *Cochrane Database Syst. Rev.* 12, CD003054 (2017).
- 6 Kahn, R. & Davidson, M. B. The reality of type 2 diabetes prevention. *Diabetes Care* 37, 943-949 (2014).
- 7 Sander, G. B. et al. Influence of organic and functional dyspepsia on work productivity: the HEROES-DIP study. *Value Health J. Int. Soc. Pharmacoeconomics Outcomes Res.* 14, S126-129 (2011).
- 8 Bytzer, P., Langkilde, L. K., Christensen, E. & Meineche-Schmidt, V. Work productivity improvement after acid suppression in patients with uninvestigated dyspepsia. *Dan. Med. J.* 59, A4461 (2012).
- 9 Nederlandse Kankerregistratie. (2999).
- 10 Zauber, A. G. et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N. Engl. J. Med.* 366, 687-696 (2012).
- 11 Hilsden, R. J., Bridges, R., Dube, C., Heitman, S. J. & Rostom, A. Scheduling rules for patients with diabetes mellitus that facilitate split-dosing improve the quality of bowel preparation for colonoscopy. *PLoS One* 12, e0182225 (2017).
- 12 Subramanian, S., Bobashev, G., Morris, R. J. & Hoover, S. Personalized medicine for prevention: can risk stratified screening decrease colorectal cancer mortality at an acceptable cost? *Cancer Causes Control CCC* 28, 299-308 (2017).
- 13 Frampton, M. J. E. et al. Implications of polygenic risk for personalised colorectal cancer screening. *Ann. Oncol.* 27, 429-434 (2016).