The Impact Of Dietary Advanced Glycation Endproducts

9 Impact (formerly known as valorization addendum)

9.1. Luckily, dietary AGEs do not worsen risk factors for T2DM.

Food processing techniques and food composition have changed massively throughout the 20th century. It is estimated that approximately 80-90% of all foods used for cooking are now already semi-processed[1]. This often involves some form of heat treatment. Many beneficial effects are associated with heat treatment, such as inactivating food borne pathogens, prolonging shelf life, increasing taste, smell, and texture, improving digestibility, but also increased consumer convenience as many of these foods are ready-to-eat[2]. However, resulting from the Maillard reaction that occurs within protein- and sugar rich heat-treated foods, AGEs are formed. As such, the modern diet represents a significant contribution to our exposure to AGEs. This may even start at a very early age, as heat-treated infant formula may contain up to 670-fold more AGEs than human breastmilk[3]. Other commonly-consumed high AGE products include bread, heat-treated cereals, meat, and confectionaries.

AGEs are most-known from their formation within the body, a process that occurs naturally with ageing[5, 6] but is accelerated in T2DM due to the presence of hyperglycemia[7]. In this context, AGEs are involved in the development of both the cardiovascular complications of T2DM[8-14] but also of T2DM itself[11, 15, 16]. From the observation that dietary AGEs may be absorbed into the circulation[17, 18], and that their presence in our modern diet is significant, it has been hypothesized that dietary AGEs may also contribute to the many biological consequences that are described for in-vivo formed AGEs. Particularly, a diet high in AGEs may be a risk factor for the development of insulin resistance and ultimately T2DM[19-23]. Interestingly, based on these previous studies, some authors have suggested that restricting dietary AGE intake may present a novel preventative treatment for the development of T2DM. Moreover, one author wrote a book on the “toxicity” of dietary AGEs and a guide on how to reduce their intake.

However, as explained in detail in Chapter 1 and 8, this conclusion may be too strong, and the work provided in this thesis, with its limitations and external validity in mind, does not support the hypothesis that dietary AGEs contribute to the development of T2DM. While this may be regarded as disappointing, as we were not able to identify a new risk factor for the T2DM epidemic, results of our studies do not underscore the need to reduce AGE intake. If this would apply, large efforts at the individual level but especially at the level of food manufacturers were needed. As explained above, AGEs are widely present in our modern diet, especially in products that are highly palatable, and individuals at risk for diabetes would have to consume less-desirable

food products that contain less AGEs. On the other hand, food manufacturers would have to construct preparation methods that retain the many beneficial effects of the Maillard reaction while simultaneously limiting AGE formation. Doing so would require extensive knowledge on the factors that drive AGE-formation in foods.

9.2. Free AGEs in urine and plasma are a short-term reflection of dietary AGE intake

From our repeated analyses of free pyrraline in urine during a 3-day low and high AGE diet in the Addendum to Chapter 6, it becomes evident that free AGEs in urine are rapidly influenced by AGE intake. Moreover, after a 4-week diet low compared to high in AGEs in Chapter 6, the increase in free AGEs in plasma is sustained after an overnight 12-hour fast. This suggests that free AGEs in plasma and urine may serve as a sensitive marker of dietary AGE intake on the very short term. However, this also has consequences for studies in which free AGEs in plasma or urine serve as an outcome of interest. Participants in clinical trials often visit the lab in the fasted state, and remain as such during the remainder of the day. Thus, it is likely that participants treat themselves to a nice (and therefore high AGE) meal the evening prior to their lab visit. Although the randomization process in a randomized controlled trial should distribute this occurrence equally over treatment arms, this will lead to inaccuracies of treatment effects. This in turn increases the number of individuals needed to detect a statistically significant difference between groups. Trials investigating the effects of an intervention, be it dietary, pharmaceutical, or exercise, should standardize intake of dietary AGEs before collecting blood or urine samples at baseline or follow-up. Although several trials investigating the effect of a low or high AGE diet on insulin sensitivity applied some sort of dietary restriction days/weeks before the baseline visit, such as restricting junk food, we are to our knowledge the only to prescribe a "normal" AGE diet two days prior to the baseline visit.

9.3. Not publishing null findings is a threat to scientific progress

The work provided in this thesis demonstrates very limited biological effects of dietary AGEs in humans, which is in stark contrast compared to several previous studies. Although this can partly be explained by methodological differences between studies, another potential explanation is that previous null findings have not been published. In a 2007 analysis of a sample of published studies over 22 disciplines, 85.9% of results were positive and in line with the hypothesis[24]. Thus, it goes without question that a serious proportion of null findings are not published. This problem is termed positive-outcome bias, and is a threat to scientific progress. The overabundance of positive findings inflates effect size estimates in meta-analyses[25] and consequently wastes recourses as researchers try to replicate non-existent findings or conduct

nonsensible follow-up studies. Although positive-outcome bias may occur at the level of a journal or of authors, it is suggested that once a manuscript is submitted, acceptance rate is similar for positive and null results[26]. As such, authors are suggested to be mainly responsible.

Positive-outcome bias occurs when authors selectively report their outcomes, or when the hypothesis is changed after the results are already known. When not all outcomes are in line with the original hypothesis, providing a theoretical background for this discrepancy is often difficult. As such, it is easier to draft a manuscript when null findings are left out. Additionally, articles with positive results are approximately two times more likely to be cited[27], which is termed citation bias, and provides another potential rationale for authors to leave out null findings. In this thesis, we report almost exclusively null findings. Our results are not in line with several other previous studies that show biological effects of a low or high AGE diet supplied for similar durations. Our extensive panel of outcomes and combined experimental and epidemiological approach emphasizes that positive-outcome bias does not apply to the work described in this thesis. Although our findings should be validated by other groups, it is evident that our approach reduces the need for several new trials.

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