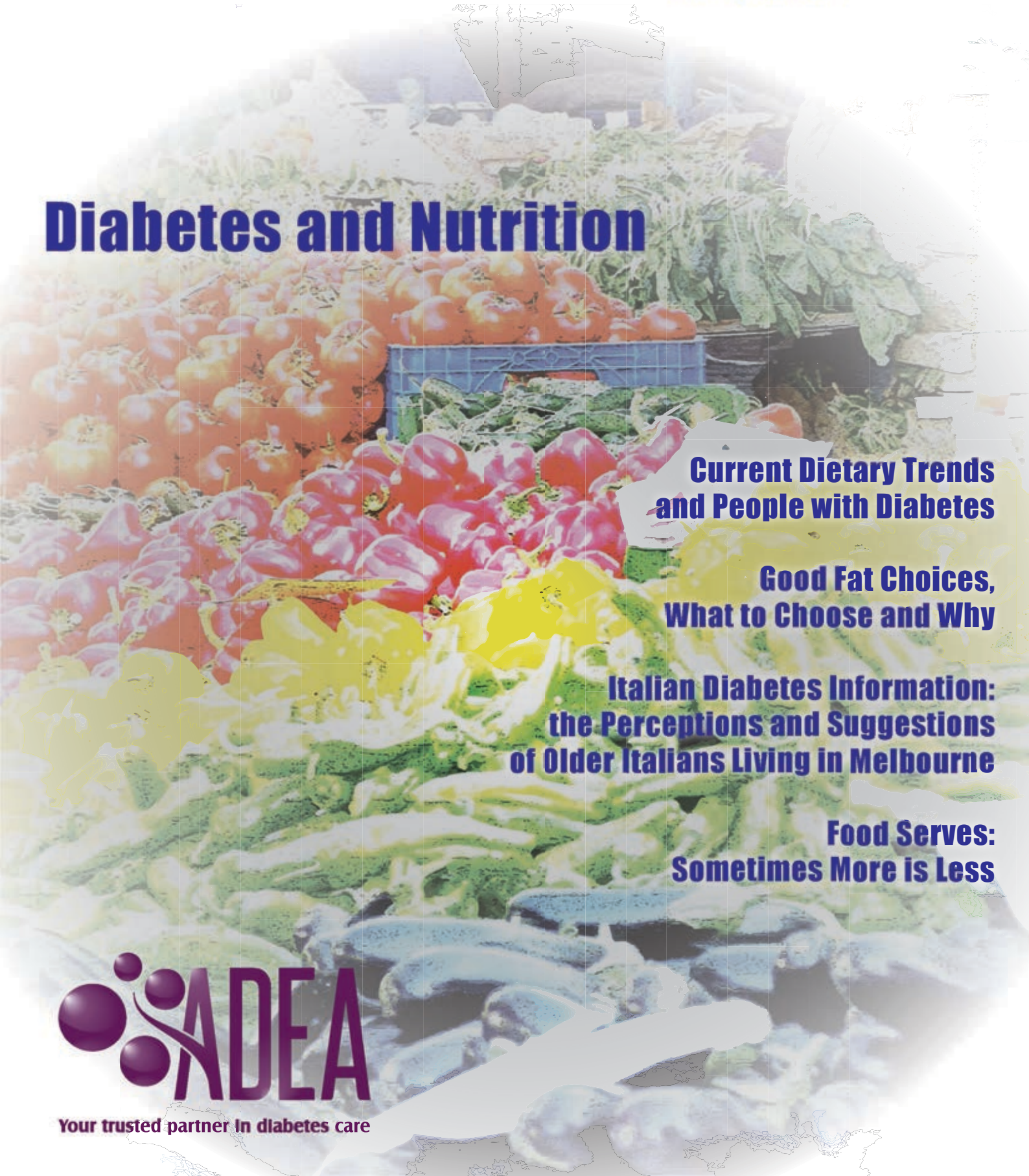
Australian
Diabetes Educator

Volume 18, Number 1, March 2015

Diabetes and Nutrition



Current Dietary Trends and People with Diabetes

Good Fat Choices, What to Choose and Why

Italian Diabetes Information: the Perceptions and Suggestions of Older Italians Living in Melbourne

Food Serves: Sometimes More is Less

ADEA

Your trusted partner in diabetes care

ADEA

Mission
To lead and advocate for best practice diabetes education and care

Vision
Excellence in diabetes support

Contents

Sustaining members

Our sustaining members make an important contribution to our ongoing growth. Their financial support assists ADEA in pursuing its goal of achieving optimal health and wellbeing for all people affected by, and at risk of, diabetes, through education, advocacy, support and research.

AstraZeneca Diabetes

novo nordisk®

Roche

Abbott Nutrition

MSD

Lilly DIABETES

SANOFI

$SGLT_2$ Inhibitors Conceptualising a New Approach to Diabetes Management

Merlin Thomas

An important focus of early diabetes management has been to eradicate glycosuria. All the classic symptoms of diabetes (dry skin, mouth and eyes, blurred vision, lethargy, headaches, thirst, polydipsia, polyuria, weight loss, etc) are driven by the excessive loss of glucose into the urine when plasma glucose levels are high. Abolishing glycosuria by effect-ively treating hyperglycaemia results in dramatic initial improve-ments in patient health and wellbeing. So why would you wish to use a pill to increase the loss of glucose into the urine?

Professor Merlin Thomas, MBChB, PhD, FRACP
NHMRC Senior Research Fellow
Baker IDI Heart and Diabetes Institute
mthomas@bakeridi.edu.au

Inhibition of $SGLT_2$

In 2013, Australia became one of the first countries in the world to approve the use of $SGLT_2$ inhibitors for the management of diabetes. These agents work by reducing the capacity of the kidneys to reabsorb glucose. The kidneys normally filter approximately 180g of glucose from the blood into the renal tubules every day. Almost all of it (99.99%) is then reabsorbed. Less than 0.1g/day ever finds its way into the toilet.[1-3] However, the capacity for reabsorption is limited. If glucose levels in the plasma rise beyond approximately 10 mM, as happens periodically in people with diabetes, the filtered glucose load exceeds the capacity for its reabsorption.[1-3] This means that glucose (and the water held with it) will spill over into the urine.

$SGLT_2$ is a transporter protein found in the early renal tubules. It is responsible for reabsorbing over 90% of glucose from the urine. $SGLT_2$ inhibitors reduce the amount of glucose reabsorbed through this pathway by about a third[4]. As a result, the threshold at which plasma glucose now escapes into the urine is lowered from around 10 mM to 8mM[5]. In someone with diabetes this means an extra 50-80g of glucose is lost from their body every day6. This loss is not inconsiderable. In energy balance terms this is equivalent to losing ~300kCal. A similar amount of calories can be lost through jogging for half an hour or walking the dog for an hour every day. Except it is now achieved simply by going to the toilet.

What are the advantages?

In people with diabetes, losing excess glucose down the drain has a number of advantages. First and foremost, $SGLT_2$ inhibitors lower HbA1c, fasting and postprandial glucose levels.[7] On average HbA1c will be reduced 0.6-1.0%7. This is roughly similar in magnitude to what can be achieved with other glucose lowering agents such as metformin, sulphonylureas and DPP4 inhibitors.[7] However, greater falls may be achieved when glucose levels are consistently high[8].

The second key advantage of $SGLT_2$ inhibition is that insulin is not needed for lowering glucose levels (i.e. $SGLT_2$ inhibition works through an insulin independent-mechanism).[6,9] This means that this strategy potentially offsets the 'work' of the pancreas to make insulin to deal with excess glucose. The same net effect may be seen with physical activity, which promotes insulin-independent muscle glucose uptake to offset insulin requirements. The long-term value of 'unloading' the beta-cells may be important for their preservation and the sustainability of glucose control, especially when compared to beta-cell exhaustion associated with sulphonylureas.[9] In advanced diabetes, the requirement for insulin injections and the dose needed can also be reduced by concomitant $SGLT_2$ inhibition.

The loss of calories into the urine also results in rapid and significant weight loss (approximately two kilograms in six months).[7] This can be especially valuable in early diabetes when weight loss is a high priority, and can be hard to achieve, reinforce or sustain with standard therapies, like sulphonylureas, insulin and pioglitazone. Importantly, most of the weight loss seen with $SGLT_2$ inhibition is loss of fat, including loss of visceral fat,[10] which is key not just for the waist-line but also for overall health.

Because little or no glycosuria occurs at normal plasma glucose levels, $SGLT_2$ inhibition does not cause hypoglycaemia. This is an important advantage, as hypo-glycaemia is frequently a major barrier to optimal glucose control. However, hypoglycaemia may sometimes be seen when $SGLT_2$ inhibition is combined with the excessive or untimely actions of sulphonylureas or insulin[11].

What about passing more urine?

Patient education and understanding are key to compliance and gaining optimal results, especially with unfamiliar agents. Even without glucose monitoring, patients know when they have taken their $SGLT_2$ inhibitors, because of the amount and frequency of urination. Increased glycosuria following taking a $SGLT_2$ inhibitor induces an osmotic dieresis so that urine output rises on average by 300-400 ml/day6. This is the same volume of fluid contained in a can of soft-drink or in a single void from a normal bladder. This means taking $SGLT_2$ inhibitors will generally cause urination once or maybe twice more every day. This is not usually a problem, especially if the medication is taken in the morning. In clinical trials of $SGLT_2$ inhibitors, only 3-5% of participants ever complained of troublesome urinary symptoms like frequency, urgency, polyuria or nocturia compared to 1-2% in placebo treated groups[12]. It was rare for the need to stop therapy. Indeed, some patients report that changes in urine output are reassuring as they know that the drug must be working. At the same time, subjects with pre-existing bladder, pelvic floor or prostate problems, will be less accommodating to any increase in their urine output, and other glucose lowering strategies should be preferred in these contexts. The modest volume losses associated with $SGLT_2$ inhibition shouldn't cause dehydration, constipation or dizziness, although systolic blood pressure levels are modestly lower (on average ~4mmHg)7. However, those prone to postural hypotension, dizziness or taking loop diuretics should also consider other glucose lowering strategies.

What about UTIs?

The presence of glucose in the urine increases the risk of urinary tract infections (UTI). UTIs are more common in diabetes, especially

in women. Glycosuria promotes bacterial growth in the urine, hampers microbial resistance and impairs bladder function. Although $SGLT_2$ inhibitors promote glycosuria, surprisingly, UTIs were not significantly more common or more severe in participants receiving $SGLT_2$ inhibitors in clinical trials7. This is possibly because people taking $SGLT_2$ inhibitors empty their bladder more often, and just like encouraging drinking, this reduces bladder stasis and offsets the risk of UTIs. Older people and those with bladder problems were generally not enrolled in clinical trials of $SGLT_2$ inhibitors, so it may also be partly selection bias. However, even in women with a previous history of chronic or recurrent UTIs, no significant increase in UTIs was seen in trials.

What about genital thrush?

The presence of glucose in the urine also increases the risk of genital thrush (candidiasis). This is a very common infection. Over 75% of all women will get thrush at least once in their lifetime. 5-8% will have recurrent episodes (>2 times a year). Diabetes increases the risk of developing thrush and using a $SGLT_2$ inhibitor further increases its incidence. About one in twelve women with diabetes using a $SGLT_2$ inhibitor will be affected5. If it does happen, it is usually in the first 3-4 months of treatment and is easy to recognise:

- Acute genital itchiness
- White vaginal discharge
- Vaginal soreness, irritation, vulvar burning, pain with sex or urination
- Odour, if present, is slight and inoffensive.

Symptoms are often worse in the week before menses. In uncircumcised men, thrush can cause balanitis (painful swelling of the end of the penis). Infections can be rapidly and easily treated with short courses of antifungal therapies (topical creams, suppositories or oral 'azoles'). Once treated, recurrent infections are uncommon. Because of this issue, women and uncircumcised men should be tactfully educated about the importance of genital hygiene and what to look out for as well as encouraged to present early in the event of any symptoms. They should also be reminded that genital mycotic infection does not mean a sexually transmitted disease (STD) as the terms are frequently confused on the internet (with awkward implications).

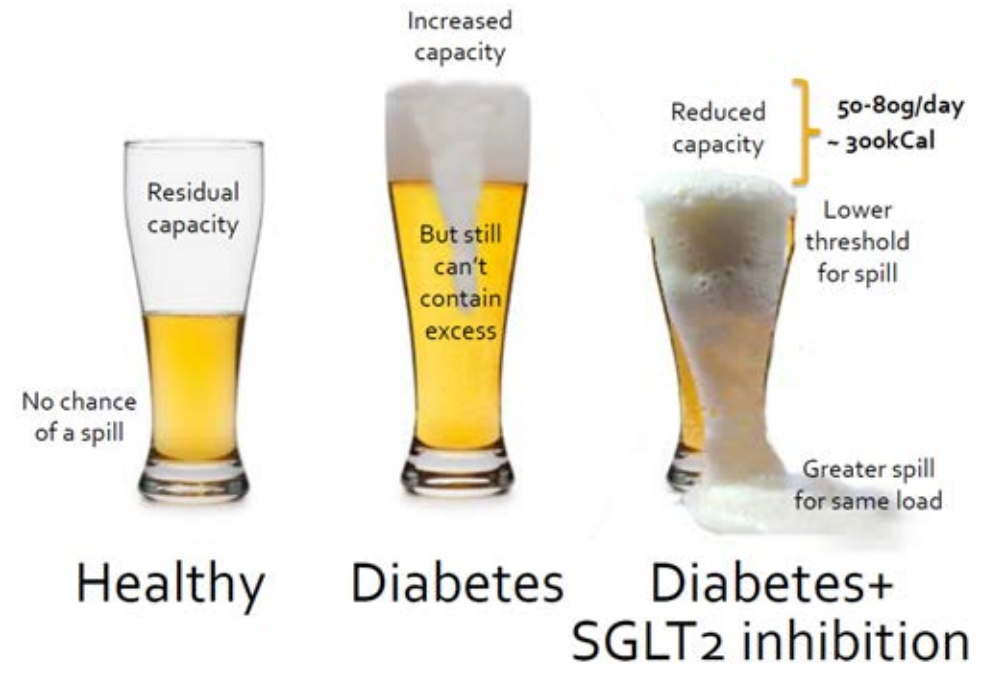


Figure Legend

Although the capacity for glucose reabsorption is increased in diabetes, it is ultimately limited so that when glucose levels rise above ~10mM, glucose spills over into the urine. Treatment with an $SGLT_2$ inhibitor simply reduces the capacity of the kidneys to reabsorb glucose, so that an extra 50-80g of glucose (~300kCal) is lost into the urine every day to improve glucose control and assist in weight management.

What about cancer?

The shadow of cancer has recently been cast across many new agents for managing diabetes, including oral therapies and insulin. Today, every new agent must go through rigorous testing to ensure the risk of cancer is not modified, and SGLT2 inhibitors are no exception. Early studies reported numerically more cases of bladder cancer in subjects treated with dapagliflozin than with standard therapy, and on this basis FDA approval for this agent was initially withheld. However, most cases already had blood in the urine before starting treatment or only a short time after starting, making a causal link unlikely. Trials of other $SGLT_2$ inhibitors have not observed any difference in cancers[13]. Moreover, $SGLT_2$ is only present in the proximal tubule of the kidney and is not found in the bladder. Finally, some people are born without $SGLT_2$, a condition known as benign familial glycosuria. And despite persistent glycosuria throughout their entire life, they remain healthy.

Just the beginning?

Although for years we have been encouraging patients to reduce their glucose levels so that glycosuria disappears, actually increasing urinary glucose loss can facilitate better diabetes control. Furthermore, the wasting of calories that would otherwise be deposited as fat is an important adjunct for many patients, especially early in their care. $SGLT_2$ inhibitors are not a panacea, or an alternative to diet and lifestyle modification. However, in the future, it is likely that they will be a common component of a multi-modal approach to comprehensive glucose control.

Competing interests:

MCT has received honoraria for educational symposia conducted on behalf of Astra Zeneca, BMS and the Boehringer Ingelheim and Lilly alliances, both manufacturers of $SGLT_2$ inhibitors

References:

1. Gerich JE, Bastien A. Development of the sodium-glucose co-transporter 2 inhibitor dapagliflozin for the treatment of patients with type 2 diabetes mellitus. *Expert Rev Clin Pharmacol*. 2011;4:669-683
2. Tahrani AA, Barnett, AH. Dapagliflozin: A sodium glucose cotransporter 2 inhibitor in development for type 2 diabetes. *DiabetesTher*. 2012;1:1-12
3. Mather A, Pollock C. Glucose handling by the kidney. *Kidney international. Supplement*. 2011:S1-6
4. Abdul-Ghani MA, DeFronzo RA, et al. Novel hypothesis to explain why sglt2 inhibitors inhibit only 30-50% of filtered glucose load in humans. *Diabetes*. 2013;62:3324-3328
5. Wilding JP. The role of the kidneys in glucose homeostasis in type 2 diabetes: Clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors. *Metabolism: clinical and experimental*. 2014;63:1228-1237
6. Kilov G, Yeung S, et al. Sglt2 inhibition with dapagliflozin: A novel approach for the management of type 2 diabetes. *Australian Family Practitioner*. 2013;42:706-710
7. Vasilakou D, Karagiannis T, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. *Annals of internal medicine*. 2013;159:262-274
8. Rosenstock J, Hansen L, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: A randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes care*. 2014
9. DeFronzo RA, Davidson JA, et al. The role of the kidneys in glucose homeostasis: A new path towards normalizing glycaemia. *Diabetes, obesity & metabolism*. 2012;14:5-14
10. Bolinder J, Ljunggren O, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *The Journal of clinical endocrinology and metabolism*. 2012;97:1020-1031
11. Sun YN, Zhou Y, et al. The efficacy of dapagliflozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: Meta-analysis of randomised controlled trials. *BMJ open*. 2014;4:e004619
12. Johnsson KM, Ptaszynska A, et al. Urinary tract infections in patients with diabetes treated with dapagliflozin. *Journal of diabetes and its complications*. 2013;27:473-478
13. Lin HW, Tseng CH. A review on the relationship between sglt2 inhibitors and cancer. *International journal of endocrinology*. 2014;2014:719578

Annual Scientific Meeting

Save the date
26 - 28
August 2015

Adelaide Convention Centre,
South Australia

Australian Diabetes Society
and
Australian Diabetes
Educators Association

ads
Australian Diabetes Society

ADEA
Your trusted partner in diabetes care

"Shake it up:
a fresh perspective on the science of diabetes"

2015 Abstract Award

ADEA is pleased to announce the following abstract awards to be presented to ADEA members who submit abstracts at the ADS-ADEA Annual Scientific Meeting this year:

BD

Roche

BD Medical Best
Oral Presentation Award

BD Medical Best
E-poster Award

Roche Best Novice
Oral Presentation Award

Roche Best
Novice E-poster Award

Roche Best
Poster Award

Roche Best
Novice Poster Award

For more information visit:
www.ads-adea.org.au

Follow us on Twitter
@ADSADEA

YouTube