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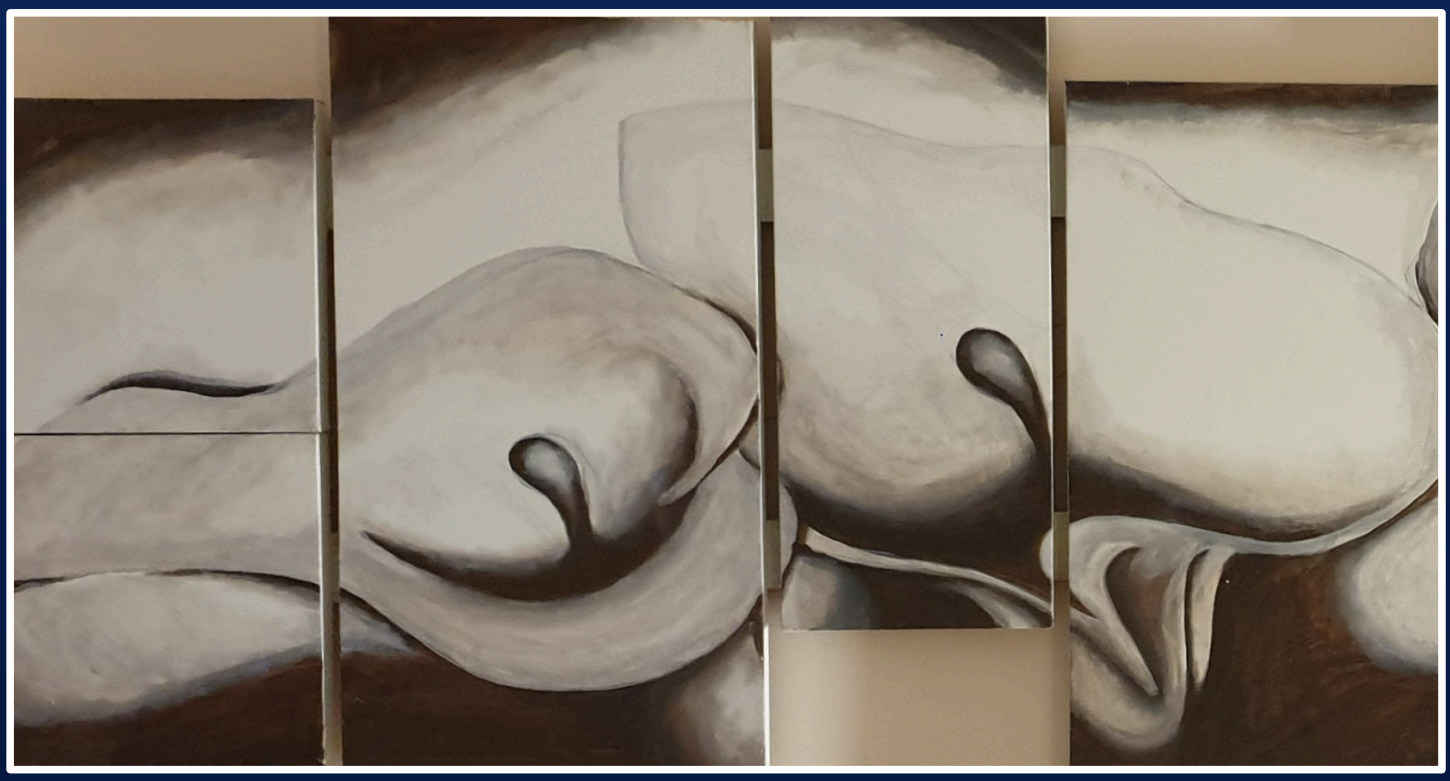

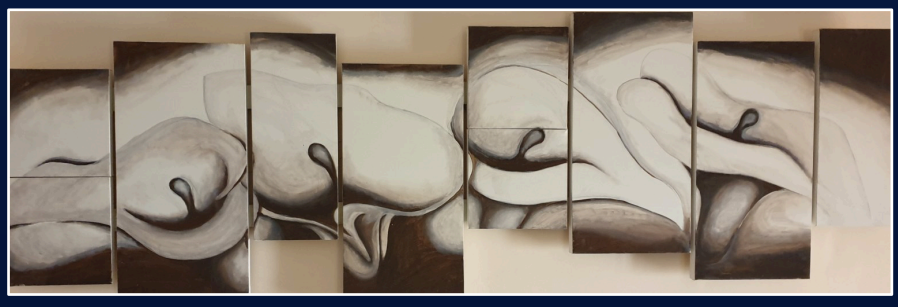

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EDITORIAL

Editorial

Simon Paul Attard Montalto

The guest editorial relates to a remarkable disregard for health and safety (H&S) at work resulting in four fatalities at the height of world war two in Malta. The author, then a seven year old boy, witnessed the event and should be commended for doggedly researching the facts, until finally revealing the sequence of events that led to this tragedy. Eighty years later, and similar events with fatalities at work continue with depressing regularity – only now, the extenuating circumstances associated with a world war that, to a large extent, allowed this lapse in safety back in 1942, simply do not exist. In contrast, in 2023, there are no excuses that can 'justify' the general sloppiness and, in many cases, the total disregard of anything to do with H&S that prevails on a daily basis in numerous workplaces in Malta. Indeed, those in authority in 2023 should learn from the lesson presented by their counterparts in 1942 who took immediate and effective action to address their own H&S crisis almost a century ago!

Simon Paul Attard Montalto
Editor
Malta Medical Journal

COVER PICTURE

'The Maltese *Ġilju*' - *Acrylic on canvas, 2.5m by 70cm*

Faye Borg Grech is an educational psychologist by profession who always had a love for art. It started as a young girl's hobby, then obtaining her ordinary and intermediate levels in art. Art is no longer just a hobby, but also an escape from the busy days and the troubling thoughts.

Ms Borg Grech obtained her degree and masters in psychology, and more recently her warrant. She works with the church schools supporting children and adolescents with any learning and mental health needs. She married her husband Luke in 2021. Due to COVID-19 restrictions, the wedding turned into an intimate and beautiful ceremony.

She is an admirer of nature and animals, especially cats. She is the proud owner of an energetic ginger tabby and a very vocal Siamese cat. Most of her artworks will involve an aspect of nature.

Fatal Aviation Fuel Exposure

Herbet M Lenicker

ABSTRACT

In 1942, 70 of 250 labourers were admitted to St Aloysius War Hospital suffering from respiratory and neurological symptoms of varying severity following inhalation of Royal Air Force (RAF) 100-octane aviation fuel fumes in a poorly ventilated Mtarfa railway tunnel. Four died later in hospital. This incident is re-visited in the light of new information, and given its implications to Health and Safety that are still relevant today.

Background

In 1942, during the height of World War Two, three quarters of St Aloysius College (SAC) in Birkirkara, Malta, was being used as a civilian hospital for men. SAC had been requisitioned by the Medical and Health Department for the duration of the war. The college theatre served as the largest ward, whilst the rest of the building and playing fields continued to be used as a Jesuit College for boys.

The author, then a seven year old was a pupil at SAC and frequently visited the hospital where his grandfather worked. During one hospital visit 80 years ago, he recalled a horrific scenario when six well-built male patients were admitted acutely in considerable distress. All were crying loudly, confused and agitated. Four of them died shortly afterwards. The author overheard that they had been handling fuel in a railway tunnel at Mtarfa, but there was no public announcement to that effect.

DOCUMENTATION

After many years of searching, a relevant report was found on the website of the Royal Army Medical Corps (RAMC) with reference to "Encephalopathy" published in the Malta Garrison Report, 1942.[1] This graphic description accurately recalls the distressing, acute clinical situation witnessed by the author in 1942, as follows:

Encephalopathy RAMC report[1]

"In Dec 1942, 70 out of 250 labourers were admitted to St Aloysius War Hospital, Birkirkara, with varying severity of neurological symptoms. Four died in hospital. The carriers and stackers had been employed by the Civil Government in unloading and stacking leaking cans of Royal Air Force (RAF) 100-Octane fuel containing tetraethyl lead (TEL) in a disused, poorly ventilated railway tunnel in Mtarfa.

The men had been working for some weeks in 12 hour shifts with an hour break for meals with two other breaks of half an hour each . . . . The carriers took ten minutes to transport a carton of two four gallon petrol cans to the end of the tunnel and another ten minutes to reach the open end for the next load.

. . . the stackers were the most affected. Mild cases had soreness of eyes and throat, headaches, nausea, and breathing difficulties. The more severely affected had vertigo, loss of power in their legs, profuse salivation, involuntary jerking of the muscles of the face and hands (myoclonus), and loss of consciousness.

One labourer aged 38 years had been working for four weeks in the tunnel prior to the onset of his symptoms. On the 15th of December 1942, he complained of giddiness, headache, difficulty in swallowing, profuse salivation and lower limb weakness. He was admitted to St Aloysius College Hospital on the 25th of December. He became delirious and incontinent with a coarse tremor of the upper limbs. He lapsed into a coma and had generalized convulsive movements for two to three days prior to his death. His post mortem showed brain oedema and petechial haemorrhages in the subthalamic region. It was concluded that the symptoms were due to intoxication from petrol fumes rather than tetra ethyl lead (TEL)".[1]

COMMENTARY

The conclusion in the post-mortem report was at variance with clinical concerns relating to TEL within the Department of Health.[1] Given the lipophilic properties of TEL, it can be absorbed through the intact skin, and TEL vapour is readily absorbed through the pulmonary epithelium. Its fat solubility allows localisation in the nervous tissues making it neurotoxic.[5] Indeed, TEL poisoning would explain several of the nervous manifestations suffered by the victims. These were not dissimilar to known

complications following severe TEL exposure and intoxication including vomiting, delusions, hallucinations, mania, psychotic behaviour, seizures, intense hyperactivity, facial contortions, cerebral oedema, encephalopathy, coma and death.

The toxic agent, RAF 100-octane fuel was developed in 1921 by Thomas Midgley Junior, at General Motors, USA. He showed that lead, made soluble in gasoline as tetraethyl lead (TEL), could quench the free radicles responsible for the 'cool' flame in engines that caused 'knocking'. This boosted engine power, especially if the octane rating of the gasoline was increased to 100 or above.[2] In practice, when used in Spitfire and Hurricane fighter aircraft engines, it afforded a significant advantage over enemy aircraft during air combat. This fuel was very expensive and had to be brought to Malta from the USA. When supplies were threateningly low, the fuel was delivered to Malta by submarine.[3]

Handling the fuel when it arrived in Malta was very challenging. According to the Operational Report on the 24.11.1942, members of the 1st Battalion of the 1st Cheshire Regiment experienced great difficulty unloading the cartons containing RAF 100-octane petrol. The fumes were very pungent, and the men could only work for a short time in the ship's hold.[3] The vital fuel was then transported inland and stored in the underground safety of the disused but poorly ventilated railway tunnel in Mtarfa.

NEW INFORMATION

A recent search in the local press revealed that the incident under review was never reported. This may have been for security reasons relating to a special fuel in that critical stage of the war. Indeed, the event occurred at the height of the air battle for Malta, when very harsh siege conditions prevailed. Nevertheless, based on information obtained from the National Archives of Malta (NAM, file 6774/42 from the Lieutenant Governor's office),[4] it is evident that safety arrangements in the Mtarfa tunnel were inadequate. Safe ventilation for the manual storage of this hazardous fuel in the tunnel was totally absent. Moreover, many of the handling procedures were carried out in conditions of prolonged exposure as well as inadequate ventilation which would not have been tolerated in peace time.[5] Maltese labourers worked for 12-hour shifts in the tunnel carrying leaking fuel cartons for ¾ of a mile. The stackers, however, remained in the same place storing fuel cartons and, not surprisingly, were more severely affected by the fumes.

The experience of similar incidents in the UK seems to have been limited to single cases of tetraethyl lead (TEL) intoxication inhalation during tank-cleaning.[5] A telegram from the fuel company, Shell, in London dated 10.7.1943 was received in Malta after the local incident occurred. This reported sickness and death in operators handling leaded fuel in under-ventilated areas.[6] The incident in Malta which led to four fatalities in 1942 seems to have been the first experience locally.

CGMO'S INTERVENTION

Although the incident is not specifically mentioned in the CGMO's Annual Reports of 1942 and 1943,[7,8] these patients were probably included under the heading 'Return of Diseases and Deaths of Inpatients in General Hospitals in Malta', as follows: "Injury due to poisonous gases 164 /1942 or due to lead poisoning 78/1943". Further clinical information is unavailable.

On the 24.10.1942, the Chief Government Medical Officer, Professor Albert V. Bernard, officially notified the Secretary to Government that several reports had been received of TEL poisoning due to handling petrol in the under ventilated Mtarfa tunnel.[9] Six men had been hospitalised and one had died up to the time of writing. He pointed out that ventilation in the tunnel was inadequate.

Professor Bernard recommended that without delay:

a) ventilation be improved

b) men engaged in this work should not work for longer than 2 hours at a stretch

c) men showing incipient signs of illness should be immediately relieved from work and

d) arrangements be made for RAF medical surveillance and attendance to be available for these men on the spot.

A rapid response and remedial action followed the CGMO's letter. Indeed, an official telephone message on 28.12.1942 reported that Lt. Col. Bartolo had withdrawn all his men from the tunnel, and that work on the tunnel ventilation shafts was ready to start on the 29.12.1942.[10]

In a letter dated 30.12.1942, Mr Nunn, Assistant to the Lieutenant Governor, HE Lord Gort, confirmed

that work should proceed forthwith with the excavation of ventilation shafts. Importantly, it was conceded that the men engaged in the fume-laden air or near the tunnel should be required to work for not more than 2 hours at a stretch and should then be relieved for 2½ to 3 hours.[11]

Following the CGMO's recommendations, the Lieutenant Governor was justifiably greatly concerned and the period of workers' exposure was immediately reduced to 2 hours.[12]

CONCLUSION

The CGMO in 1942, Professor Bernard, should be commended for enforcing safer working conditions for the Maltese handlers, by limiting the hazards of inhalation of the toxic fuel fumes. Similarly, the prompt and decisive response of H.E. Lord Gort, to prevent further hazardous exposure to the toxic fuel fumes despite the prevailing dire siege situation in the country at the time was remarkable.

ACKNOWLEDGEMENTS

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REVIEW ARTICLE

Emerging Trends in Diabetes: An Update on the Role of Sodium-Glucose Co-Transporter 2 Inhibitors

Desiree Seguna, Stephen Fava

The incidence of type 2 diabetes mellitus continues to rise world-wide, highlighting the need for better treatment of this condition. The last few decades have seen the emergence of several new anti-diabetic agents. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are novel oral hypoglycaemic agents that have only recently been added to the local government formulary list. We hereby discuss the mechanism of action of this oral class of agents and highlight their role and indications in clinical practice. This review provides a detailed summary of the available cardiovascular outcome trials and how these recommendations have been included in the most recent international guidelines. Finally we highlight the adverse events and contraindications of this class of agents and discuss possible future roles for SGLT-2 inhibitors.

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Diabetes poses an ongoing threat to health and economy. According to the International Diabetes Federation (IDF), the estimated prevalence of type 1 (T1D) and type 2 diabetes (T2D) in people aged 20-79 years has risen from 4.6% of the global population in the year 2000 to 9.3% in the year 2019.[1]

The treatment of T2D is challenging, with early diagnosis and access to appropriate care being pivotal to the management of the disease and prevention of secondary complications. T2D is characterised by progressive β-cell failure requiring intensification of treatment. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are novel oral hypoglycaemic agents that block the SGLT2 co-transporter located in the proximal renal tubule. Consequently, these agents lower serum glucose by enhancing its excretion and by blocking its reabsorption from urine. The results are improved glycaemic control and reductions in blood pressure and weight. The glucose-lowering activity of SGLT2 inhibitors is proportional to the ambient glucose levels and the estimated glomerular filtration rate (eGFR). Therefore, greater losses of glucose take place in patients with hyperglycaemia, whereas in patients with euglycaemia the response to treatment is attenuated leading to a lower incidence of hypoglycaemia.

As with any novel treatment, their safety profile remains under rigorous assessment. At present, concerns have arisen around the risk of amputation,

diabetic ketoacidosis (DKA), acute kidney injury (AKI), urinary tract infections (UTIs), bone fractures and cancer. It is hence important that patients are carefully selected based on pre-existing risk factors and foreseeable benefits of treatment.

CLINICAL BENEFITS & INDICATIONS

The sodium glucose co-transporter 2 is expressed in the renal proximal tubule where it reabsorbs ~90% of the filtered glucose load.[2] SGLT2 receptor inhibitors are novel glucose-lowering agents which improve hyperglycaemia by promoting renal excretion of glucose. Their glucose lowering effect is non-insulin mediated and is limited by the filtered load of glucose and the osmotic diuresis that ensues.[2]

Their usefulness in clinical practice can be described in terms of their various outcomes.

Glycaemic Efficacy

SGLT2 inhibitors have modest glucose-lowering effects. Meta-analyses comparing them with placebo found that SGLT2 inhibitors reduced HbA1c by up to an additional 0.7%.[3-6]A systematic review showed that the combination of metformin plus SGLT2 inhibitors lowered HbA1c by a further 0.61% compared with metformin alone.[7]

Weight Loss

The resulting glucosuria results in a net loss of 200–300 kcal/day.[2,8] A reduction in body weight follows the depletion of hepatic glycogen stores, as well as the water loss resulting from the accompanying osmotic diuresis. In the longer term, loss of mesenteric and subcutaneous adipose tissue further contributes to weight loss.[9] A meta-analysis comparing SGLT2 inhibitors with placebo, demonstrated a mean weight reduction of 2.99 kg at two years in the SGLT2 inhibitors group.[6] Compared with metformin monotherapy, the combination of metformin and SGLT2 inhibitors resulted in an additional weight reduction of 2.0 kg.[7]

In insulin-treated patients, the addition of an SGLT2 inhibitor decreased the total daily insulin requirement, mitigating the insulin-associated weight gain.[10] The combination of insulin plus dapagliflozin was associated with a weight reduction of 0.9-1.4 kg, compared to insulin plus placebo, which resulted in weight gain.[11]

The DEPICT-1[10] and DEPICT-2[12] (Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes) trials, evaluated the long-term safety and efficacy of dapagliflozin as an adjunct to insulin in patients with inadequately controlled type 1 diabetes (T1D). Compared with placebo, dapagliflozin led to significant reductions in total daily insulin dose requirements, HbA1c and weight.[10] Dapagliflozin became the first oral medication approved by the National Institute for Health and Clinical Excellence (NICE) as an adjunct to insulin, for the treatment of inadequately controlled T1D in adults with a BMI ≥ 27 kg/m^2.[13] However, in November 2021 NICE withdrew this licence.

Cardiovascular Outcomes

Atherosclerotic Cardiovascular Disease (ASCVD)

Following concerns of a higher risk of myocardial infarction (MI) conferred by rosiglitazone[14], the US Food and Drug Administration (FDA) issued a guidance for industry to perform cardiovascular outcomes trials (CVOTs) for new drugs intended to improve glycaemic control in T2D.[15] In line with this, a number of long-term prospective CVOTs have subsequently been undertaken and published.

The EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes) assessed the effect of empagliflozin vs placebo on cardiovascular outcomes in patients with T2D and established ASCVD. Empagliflozin reduced the risk of major adverse cardiovascular events (MACE) (a composite endpoint of death from cardiovascular causes, non-fatal MI and non-fatal stroke) by 14%, cardiovascular death by 38% and all-cause mortality by 32%. Unlike glucagon-like peptide-1 receptor agonists (GLP-1RA), the reduction in the risk of MACE with empagliflozin was almost exclusively accounted for by the effect on the cardiovascular death component, as empagliflozin did not reduce non-fatal MI or non-fatal stroke.[16]

In the CANVAS Program (Canagliflozin Cardiovascular Assessment Study and Canagliflozin Cardiovascular Assessment Study - Renal), treatment with canagliflozin significantly reduced the risk of MACE (cardiovascular death, non-fatal MI and non-fatal stroke), which was recorded in 26.9 vs 31.5 participants per 1,000 patient-years of the canagliflozin and placebo groups, respectively. Treatment with canagliflozin was, however, associated with an increased risk of amputation (6.3 vs 3.4 participants per 1,000 patient-years).[17] In the CREDENCE (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation) trial, treatment with canagliflozin was again associated with a lower composite risk of

cardiovascular death, non-fatal MI, or non-fatal stroke.[18]

The DECLARE-TIMI 58 study (Dapagliflozin Effect on Cardiovascular Events Thrombolysis in Myocardial Infarction), assessed the effects of dapagliflozin vs placebo on cardiovascular and renal outcomes in patients with T2D and established ASCVD or multiple risk factors for ASCVD.[19] Dapagliflozin was non-inferior to placebo with regards to MACE (cardiovascular death, non-fatal MI and non-fatal stroke), but reduced a composite of cardiovascular death and hospitalisation for heart failure. This was largely driven by a lower rate of hospitalisation for heart failure as there was no difference in cardiovascular death between the groups. Compared with the EMPA-REG OUTCOME trial[16] and the CANVAS Program[17], the DECLARE-TIMI 58 trial had a lower fraction of participants with established ASCVD and a greater proportion of patients with multiple risk factors for ASCVD, possibly partly explaining the differences in ASCVD outcomes.[19] In a sub-analysis of the primary trial, dapagliflozin decreased cardiovascular outcomes.[20]

The VERTIS CV trial, compared ertugliflozin to placebo in patients with T2D and prevalent CVD disease. Ertugliflozin was associated with a reduction in hospitalisation for heart failure but was non-superior to placebo with regards to death from cardiovascular causes, non-fatal MI, or non-fatal stroke.[21]

Heart Failure

A reduced incidence of heart failure has been reported with the use of empagliflozin,[16,22] canagliflozin[17], dapagliflozin[19]and ertugliflozin.[21]

In EMPA-REG OUTCOME trial, treatment with empagliflozin was accompanied by a 35% reduction in hospitalisation for heart failure when compared with placebo.[16] Similarly, the CANVAS Program[17] and DECLARE-TIMI 58 trial[19]reported reductions in rates of hospitalisation for heart failure of 33% and 27% with canagliflozin and dapagliflozin, respectively. Additional data from the CREDENCE trial with canagliflozin, showed a 39% reduction in hospitalisation for HF.[18]

The majority of patients in all of these study populations did not have HF at baseline (rates of HF 10-14%).[23] However, a subsequent report from the EMPA-REG OUTCOME trial confirmed that empagliflozin consistently improved HF outcomes in patients with and without a previous history of HF.[22]

The DAPA-HF study (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), was conducted in patients with pre-existing heart failure (New York Heart Association [NYHA] class II, III, or IV) and an ejection fraction of <40%. Fifty-eight % of participants did not have a history of T2D. Over a median of 18.2 months, the primary outcome (a composite of worsening HF necessitating hospitalisation or intravenous therapy, or cardiovascular death) occurred in 16.3% vs 21.2% of participants in the dapagliflozin and placebo group, respectively. This effect was consistent, irrespective of the presence or absence of T2D.[24]

The EMPEROR-Reduced trial compared the effects of empagliflozin with placebo in patients with HF and a reduced ejection fraction (HFrEF), with or without diabetes and who were already on standard care for HF. Over 16 months, the primary outcome event (a composite of hospitalisation for worsening HF or cardiovascular death) occurred in 19.4% vs 24.7% of patients in the empagliflozin and placebo group, respectively. This effect was consistent irrespective of the presence or absence of T2D. Compared with placebo, empagliflozin also reduced total HF hospitalisations and adverse renal outcomes.[25]

The DAPA-HF[24] and EMPEROR-reduced[25] trials, extend the benefits of SGLT2 inhibitors in patients with HFrEF but *without* diabetes. The exact mechanisms underlying the reduction in HF hospitalisations with SGLT2 inhibitors remain to be elucidated but cannot only be explained by the modest glucose, weight and blood pressure lowering effects of this class of drugs.

The EMPEROR-preserved trial looked at the effect of empagliflozin on morbidity and mortality, in patients with or without T2D and HF with preserved ejection fraction (HFpEF).[26] Empagliflozin brought about a reduction in cardiovascular death and hospitalisation for heart failure in patients with HFpEF, regardless of the presence or absence of T2D.[26]

In the VERTIS CV trial, rates of hospitalisation for heart failure were lower with ertugliflozin compared to placebo, at 2.5% vs 3.6% respectively.[21]

Renal Outcomes

Initial data on canagliflozin from the CANVAS Program suggested a beneficial effect of canagliflozin compared with placebo on progression of albuminuria and a composite of reduction in eGFR, need for renal replacement therapy or death from renal causes.[17] These findings did not, however, reach statistical significance. Subsequently, the CREDENCE

study was designed to specifically assess the effects of canagliflozin on renal outcomes in patients with T2D and albuminuric stage 3 chronic kidney disease (CKD).[18] Compared with placebo, canagliflozin showed a risk reduction of 30% in a composite renal endpoint of a) end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2), b) doubling of serum creatinine, c) or death from cardiovascular or renal causes. The trial was stopped early due to conclusive evidence of efficacy.

The EMPA-REG OUTCOME trial, showed that compared with placebo, empagliflozin reduced the risk of incident or worsening nephropathy (defined as a composite of urine albumin creatinine ratio (UACR) > 300 mg/g, doubling of serum creatinine, end-stage renal disease [ESRD], or death from ESRD) by 39%.[27]

In the VERTIS CV trial there was no statistically significant reduction in the composite renal endpoint (renal replacement therapy, doubling of serum creatinine, death from renal causes) in the ertugliflozin group. However, the trend was similar to that seen with other SGLT2 inhibitors.[21]

In the DECLARE-TIMI 58 study, the renal outcome (a composite of a sustained decrease of 40% or more in eGFR to <60 mL/min, new ESRD, or death from renal or cardiovascular causes), occurred in 4.3% and 5.6% of patients in the dapagliflozin and placebo group, respectively.[19]

The DAPA-CKD trial investigated the effect of dapagliflozin on renal outcomes in patients with CKD, with or without T2D. The primary outcome (a composite of sustained decline in eGFR of ≥50%, ESRD, or death from renal or cardiovascular causes), occurred in 9.2% vs 14.5% of patients in the dapagliflozin and placebo group, respectively.[28] This trial suggests a role for SGLT2 inhibitors in reducing renal outcomes in patients with, as well as *without* T2D.

ADVERSE EVENTS & CONTRAINDICATIONS

Amputations

The CANVAS Program reported a two-fold risk of lower limb amputations (mainly toe and midfoot) in the canagliflozin group compared with placebo.[17] Those most at risk had a previous history of amputation, peripheral vascular disease, or neuropathy. The CREDENCE trial, however, showed no significant increase in lower limb amputations.[18]Likewise, a *post hoc* analysis of the EMPA-REG OUTCOME trial, showed no increased risk of lower limb amputation.[29]

A pharmacovigilance study using the WHO global database of individual case safety reports (VigiBase), reported an increased risk of toe amputations with canagliflozin, empagliflozin, and dapagliflozin (proportional reporting ratios 7.09, 4.96, and 2.62 respectively).[30] In view of these concerns, SGLT2 inhibitors should be avoided in high-risk patients.

Diabetic Ketoacidosis (DKA)

SGLT2 inhibitors–associated DKA, has been reported in patients with both T1D and T2D.[31] It may be accompanied by euglycaemia, in which case delayed recognition often ensues. Serum or urine ketones should be checked in patients taking SGLT2 inhibitors presenting with nausea, vomiting, malaise or a metabolic acidosis.

In a review of patients with T1D taking SGLT2 inhibitors, 5% developed DKA while 10% developed ketosis.[31] In patients with T2D, DKA rates ranged from 0.16-0.76 events per 1,000 patient-years.[32,33] The CREDENCE trial, reported an increased risk for DKA at 2.2 events per 1,000 patient-years in the canagliflozin group, compared with 0.2 events per 1,000 patient-years with placebo.[18]The risk of DKA is higher amongst patients who have been on SGLT2 inhibitors for >52 weeks and in those aged ≥60 years.[34]

The FDA issued a warning for SGLT2 inhibitors-induced DKA and recommends stopping temporarily before planned surgery.[35] The Scottish Intercollegiate Guidelines Network (SIGN) also recommends temporary withdrawal in high-risk patients including those with low endogenous insulin secretion, states of increased insulin requirement (alcohol misuse, illness or surgery) or dehydration.[8] The European Medicines Authority (EMA) recommended listing DKA as a rare adverse reaction.[36]

Hypoglycaemia

Since the effects of SGLT2 inhibitors are independent of pancreatic β-cell function, this class of agents pose a low risk of hypoglycaemia. However, when combined with hypoglycaemic agents such as insulin or insulin secretagogues, SGLT2 inhibitors may then potentiate the risk of hypoglycaemia.[4] A meta-analysis found no difference in hypoglycaemia risk between metformin and SGLT2 inhibitors monotherapy.[7]

Genitourinary Tract Infections

An increased incidence of genitourinary tract infections has been reported with SGLT2 inhibitors, with odds ratios ranging from 3.21 (95% CI, 2.08-4.93)

for dapagliflozin 2.5 mg to 5.23 (95% CI, 3.86-7.09) for canagliflozin 300 mg.[37] This did not, however, translate into a higher risk of serious or upper urinary tract infections.[38] A previous history of genital fungal infection conferred a higher risk of same with dapagliflozin.[39]

Following 55 reports of Fournier's gangrene, the FDA issued a warning on necrotizing fasciitis of the perineum in patients taking SGLT2 inhibitors.[40]

Hypotension

Studies with SGLT2 inhibitors have reported significant reductions in both systolic and diastolic blood pressures of −4.0 mmHg (95% CI, −4.4 to −3.5) and -1.6 mmHg (0.88-3.5 mmHg) respectively.[41] Initial reductions in BP are likely secondary to the osmotic diuresis and subsequent reduction in intravascular volume.[42] Long-term reductions in BP are likely to result from inhibition of the renin-angiotensin aldosterone system or from the accompanying weight loss.[42] This effect is augmented in older patients and in patients on diuretics, ACEIs or ARBs, resulting in an increased risk of symptomatic hypotension.[43]

Acute Kidney Injury

From March 2013 to October 2015, the FDA received 101 reports of AKI in patients on dapagliflozin and canagliflozin, some of which necessitating hospitalisation and dialysis.[44] Around 50% of cases occurred within one month of commencing treatment and discontinuation led to improvements in eGFR in most cases. It is unknown whether patients had pre-existing CKD. An analysis by Nadkami *et al.* did not report an increased risk of AKI with SGLT2 inhibitors use.[45]

Renal function should be assessed prior to commencement of treatment and should be monitored thereafter. SGLT2 inhibitors should not be used for the treatment of hyperglycaemia in patients with an eGFR <45 mL/minute/1.73 m^2[46] Cautious use is warranted in high-risk patients with HF, liver failure, evidence of hypovolaemia or patients taking diuretics, NSAIDs, ACEI or ARBs.[46]

Bladder Cancer

There is no long-term safety data on the effects of the glucosuria accompanying SGLT2 inhibitors. There was a suggestion that some SGLT2 inhibitors may increase the risk of bladder cancer, particularly empagliflozin. These findings did not, however, reach statistical significance.[48] Initial data on dapagliflozin hinted to a possible increased risk of bladder and breast cancer[48], however, data from the DECLARE-TIMI 58 trial did not support this finding.[19]

Bone Fracture

There is conflicting evidence on the incidence of fractures with SGLT2 inhibitors therapy. In the CANVAS Program, fracture rates were 26% higher with canagliflozin compared with placebo.[17] However, the CREDENCE trial did not show significant differences in rates of fracture between canagliflozin and placebo.[18]A meta-analysis found similar fracture rates with canagliflozin, empagliflozin and dapagliflozin, at around 1.59% vs 1.56% in controls. The events, however, did not reach statistical significance.[47]

Use of canagliflozin has been associated with increased bone turnover markers and decreased total hip bone mineral density.[49,50] Falls resulting from secondary hypotension may contribute to fracture risk.[17]

GUIDELINE RECOMMENDATIONS

In the light of the compelling evidence provided by the CVOTs, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued a 2019 update on the "Management of hyperglycaemia in type 2 diabetes".[51] In its statement, the ADA/EASD recommended the use of SGLT2 inhibitors (or GLP-1 receptor analogues) in patients with T2D and established ASCVD.[51] The ADA/EASD further stated that the level of evidence for SGLT-2 inhibitors in T2D was greatest in patients with or without established ASCVD, but with HFrEF (EF <45%) or CKD (eGFR 30 to <60 mL/ min/1.73 m^2 or UACR >30 mg/g (and particularly >300 mg/g).[51]

In patients with T2D and HF (particularly those with HFrEF), SGLT2 inhibitors are recommended in order to reduce HF, MACE, and CV death.[51] In patients with T2D and CKD, SGLT2 inhibitors are recommended to prevent CKD progression, HF, MACE, and CV death.[51] The ADA/EASD recommends initial treatment with lifestyle therapy and metformin, unless contraindicated or not tolerated.[51] This should be followed by the addition of an SGLT2 inhibitors (or GLP-1 receptor analogue) with proven cardiovascular benefit, independent of HbA_{1c}.[51] Use in patients at high risk for amputation or with foot ulcers should only take place following careful, shared decision-making and comprehensive foot care education.[51]

The 2020 consensus statement by the American Association of Clinical Endocrinology (AACE) and the

American College of Endocrinology (ACE), states that in the presence of ASCVD (established or at high risk for), CKD stage 3, or HFrEF, SGLT2 inhibitors (or long acting GLP-1 receptor analogues) with proven efficacy may be preferred over metformin as initial therapy, irrespective of glycaemic control.[52]

According to SIGN, SGLT2 inhibitors with proven cardiovascular benefits can be added to metformin in patients with T2D and established ASCVD.[8]

NICE recommends the use of SGLT2 inhibitors as monotherapy in adults with T2D when metformin is contraindicated or not tolerated and lifestyle interventions fail AND only if a DPP-4 inhibitor would otherwise be prescribed AND a sulfonylurea or pioglitazone is not appropriate.[53]

PRESCRIBING PATTERNS

Following the emergence of compelling evidence from CVOTs, many international bodies have updated their guidelines to clearly define the role of novel agents in the management of T2D.[51,52]

Metformin, alongside lifestyle interventions, remains the preferred initial choice of therapy, unless contraindicated or not tolerated.[8,51-54] Prescribing trends for metformin are hence unlikely to change. On the other hand, prescriptions for sulfonylureas have decreased substantially from 53% in 2010 to 29% in 2017.[55]

In selected high-risk patients, 2020 guidelines recommend SGLT2 inhibitors or long-acting GLP-1 receptor analogues, independent of glycaemic control.[51,52] We hope that this will translate in increased and earlier prescribing of these medications in clinical practice. It is important to note that when combined with insulin or sulfonylureas, SGLT2 inhibitors may potentiate the risk of hypoglycaemia.[4] Therefore, the combination of SGLT2 inhibitors and insulin should be accompanied by a reduction in the total daily dose of insulin prescribed.[10] Given the modest glycaemic effect of SGLT2 inhibitors, it is very unlikely that their use will, however, allow complete cessation of previously established insulin therapy.[7]

LOCAL PERSPECTIVE

SGLT2 inhibitors have recently been added to the Maltese government formulary list for use in T2D patients with an HbA1c between 7% and 10% despite treatment with metformin, sulfonylurea or repaglinide. Patients must have either established ASCVD, HF or CKD (defined as diabetes with micro/macroalbuminuria or an eGFR <60 mL/min/1.73m^2, or both) OR a body mass index (BMI) >30 kg/m^{2}in patients who need to lose weight or in whom weight gain minimisation is necessary.[56]

FUTURE DIRECTIONS

SGLT2 inhibitors have demonstrated a clear benefit in patients with cardiorenal disease, however, they are associated with only modest improvements in glycaemia. They are costly and long-term safety implications of glucosuria are unknown. Monitoring for peripheral vascular disease, urogenital infections, hypovolaemia and decline in renal function, needs to be ongoing.[57]

Evolving data has suggested a role for SGLT2 inhibitors in the treatment of patients with HFrEF[24,25] or CKD[28] but *without* diabetes. The EMPEROR-preserved has furthered our knowledge into the role of SGLT2 inhibitors in patients with or without diabetes and HFpEF.[26] Future studies are needed to understand the role of SGLT2 inhibitors in patients with T2D but *without* established cardiorenal disease.

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REVIEW ARTICLE

Recent population studies on the prevalence and bilaterality of the fabella

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The fabella is a sesamoid bone found in the gastrocnemius muscle that is present in about 10-30% of all humans. There are however strong variations between different ethnics groups. The current review summarizes the literature regarding the prevalence and laterality of the fabella in recently published population studies. Six eligible population studies published in 2020 and 2021 were identified that investigated the prevalence of the fabella in Chinese, Korean, Nigerian, Omani and Turkish populations. The fabella prevalence rate in the included studies ranged from 11.1 to 57.2%. However, like in past research, there were significant variations between different populations in recent studies. Unfortunately, only a selected number of the recently published studies reported on the percentage of fabellae that present uni- or bilaterally. The percentage of cases that showed a bilateral fabella ranged from 27.1 to 78.8%.

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Sesamoid bones are small bones that have an important role in supporting the joints. Despite there being still a lot to be discovered about their embryology, one study identified that several sesamoid bones arose from Sox9- and Scx-positive chondroprogenitors.1 The authors state that sesamoid bones can develop independent from long bones and that the induction of their development is not dependent on the mechanical load. They concluded that several genetic and mechanical regulation mechanisms interplay in sesamoid bone development.

The fabella is a sesamoid bone found in the gastrocnemius muscle. One hypothesis about its function is that it plays a role in stabilizing the medial femoral condyle and the associated muscles and ligaments of the posterolateral corner of the knee.[2,3] In humans, in the majority of cases, the fabella presents bilaterally.[4,5] There also does not seem to be a difference in prevalence between males and females.[5,6] Several studies also reported that there was no relationship with the age of an individual [5,6], whilst other do see a difference.[7,8]

The bone is present in about 10-30% of all humans.[5,8] However, there are strong variations between different ethnics groups. The prevalence in Asian populations has been described to be higher than in other populations.[9,10] The prevalence has been also been described to have increased in the last 150 years.[5]

Several studies have investigated, amongst others, the prevalence of the fabella in different populations.[4,6,7,9-12] Additionally, two systematic

reviews were published that described the prevalence, clinical implications, differential diagnoses and other aspects of the entity.[5,8] These reviews describe several aspects of the entity from studies published between 1875 and 2020. A large number of studies were identified in these reviews. Therefore, it can be assumed that since 2020, several other populations studies have been published. To investigate these more recent publications, the objective of the current paper is to summarize the results regarding the prevalence and bilaterality of the fabella in recent population studies.

METHODS

The MedLine database (through PubMed) and Google Scholar were searched with the keyword "Fabella" until and including March 2022. Additionally, the indices of Journal of Anatomy, Anatomical Record and Journal of Morphological Sciences were manually searched for articles potentially eligible for inclusion. Based on titles and abstracts, papers were selected for potential inclusion. The full text of the selected publications were read and included if they:[1] described a study of the fabella in a specific population,[2] at least mentioned the prevalence in this population and[3] were published in 2020, 2021 or (before April) 2022. The references of the included publications were searched to identify further potentially eligible literature.

IDENTIFIED LITERATURE

Eight eligible population studies published in 2020,2021 and early 2022 were identified. They investigated the prevalence of the fabella in Chinese, Korean, Nigerian, Omani and Turkish populations.[7,13-21] The data extracted from these studies are shown in Table 1. All studies had a retrospective design and used either radiography or MRI to assess the presence of the fabella. The average number of subjects ranged widely from 377 to 2126. Several publications also mentioned the number of knees that were investigated, this ranged from 119 to 4,252.

Table 1 *Data from the included studies*

Reference	Population	Detection Method	Number of subjects/knees	Prevalence	Laterality
Adedigba et al, 2020	Nigerian	Radiography	377 subjects	45 / 377 (11.94%)	32 / 45 (72.2%) bilateral
Akdeniz et al, 2021	Turkish	MRI	531 subjects	59 / 531 (11.1%)	Not known
Akkoc et al, 2022	Turkish	Radiography	2035 subjects	605 / 2035 (29.7%)	351 / 2035 (17.2%) bilateral
		MRI	121 subjects	47 / 121 (38.8%)	
Al Matroushi et al, 2021	Omani	Radiography	813 knees	196 / 813 (24.1%)	Not known
Al Matroushi et al, 2021	Omani	MRI	119 knees	24 /119 (20.2%)	Not known
Hur et al, 2020	Korean	Radiography	2126 subjects 4252 knees	1215 / 2126 (57.2%) 2172 / 4252 (51.1%)	78.8% bilateral
Sari et al, 2021	Turkish	Radiography	1000 subjects	243 / 1000 (24.3%)	56.38% bilateral
Unluturk et a., 2021	Turkish	MRI	1000 subjects	155 / 1000 (15.5%)	27.1% bilateral
Xu et al, 2020	Chinese	MRI	732 subjects 833 knees	48.38%	Not known
Zhong et al, 2022	Chinese	MRI	979 subjects 1011 knees	402 / 1011 (39.8%)	Not known

PREVALENCE AND LATERALITY

The fabella prevalence rate in the included studies ranged from 11.1 to 57.2%. However, like in past research, there were significant variations between different populations in recent studies.

The prevalence in the Nigerian population was 11.94%.[13] This is a significant result, because in contrast with other regions, relatively little research has been done into the prevalence of the fabella in African populations.[5,8] The identified prevalence rate is however similar to the 9.8% identified in a West-African population and 15.07 - 17.65% in South Africa.[18, 22, 23]

Two studies in the Turkish population yielded a very similar prevalence, namely 11.1 and 15.5%.[14,16] These results are broadly in line with a 2017 study that reported a prevalence of 19%.[24] Another included study, published in 2022, yielded a higher prevalence of 29.7 and 38.8% using radiography and MRI, respectively.[20] This is more in line with another recent study that estimated a higher prevalence of 24.3%.[19]

A 2021 study assessed the fabella's prevalence in the Omani population in two separate ways, yielding prevalence rates of 24.1 and 20.2%. Unfortunately, no previous studies in this population were identified to allow for a comparison.

A study into the Korean population identified a prevalence of 57.2%.[15] This is more than an older study that reported a 31% prevalence rate.[25] However, a recent study found a very similar prevalence of 52.83%.[5]

Finally, two studies in the Chinese population found a prevalence rate of 48.38% and 39.8%.[17,21] This percentage is supported by another study that reported a very similar high prevalence rates in Chinese participants of 48.6%.[26]

Unfortunately, only a selected number of the recently published studies reported on the percentage of fabellae that present uni- or bilaterally. The percentage of cases that showed a bilateral fabella ranged from 27.1 to 78.8%. However, the in all but one study, the majority of cases presented bilaterally. This is in line with previous observations.[2]

CONCLUSION

Based on the number of studies identified, it is clear that fabellar prevalence rate in specific populations is still a research domain of interest. In the recently published studies included in the current review, additional data was generated for populations previously investigated. For the Chinese, Omani and Korean populations, the new studies confirm the prevalences that previous research established. For the Turkish population, mixed results were obtained. Further research should be conducted to identify potential causes for this variation in results.

The recent studies have also generated new data in populations that were previously understudied, such as the African population. Further research is needed to confirm these findings.

In general, the recent studies support the conclusion that the fabella is more prevalent in Asian populations. There was a lot of missing data in several studies regarding the laterality of the fabella. Dedicated studies should be conducted to further assess the (bi)laterality in different populations and contributing factors.

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