Project Title

Association Between Long Term Use of Sodium-glucose Co-transporter-2 (SGLT2) Inhibitors and Cognitive Function in a Longitudinal study

Project Lead and Members

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Organisation(s) Involved

Khoo Teck Puat Hospital, Admiralty Medical Centre, National Healthcare Group Polyclinics

Healthcare Family Group Involved in this Project

Medical

Specialty or Discipline (if applicable)

Geriatric Medicine

Project Period

Start date: Sept 2014

Completed date: Jan 2019

Aims

To explore the longitudinal association between sodium-glucose cotransporter-2 inhibitors (SGLT2i) use and cognitive function in patients with type 2 diabetes mellitus (T2DM)

Background

SGLT2i reduces the risk of cardiovascular and renal failure. Recent mouse models showed promising results of SGLT2i in ameliorating T2DM-induced ultrastructural remodeling of neurovascular unit and neuroglia. Hitherto, there is no published study on association between SGLT2i use and cognitive function in patients with T2DM.

Methods

This was a prospective study of 428 patients from the Singapore Study of Macro-angiopathy and Micro-vascular Reactivity in Type 2 Diabetes (SMART2D) cohort over a follow-up period of up to 6.4 years. Data on SGLT2i use was derived from questionnaire and verified with clinical database. Cognition was assessed with Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) on five domains – immediate memory, delayed memory, visuo-spatial/construction, language and attention. Multiple linear regression was performed to examine the association between SGLT2i use and rate of RBANS score change, adjusting for demographics, education, clinical covariates, baseline RBANS score and presence of APOE Ɛ4 allele.

Results

The participants' mean age was 61.1 ± 6.8 years. There were 165 patients (38.6%) using SGLT2i – 115 (26.9%) for <5 years and 50 (11.7%) for ≥5 years. In the unadjusted analysis, ≥5 years SGLT2i use was positively associated with increase in RBANS score in immediate memory (coefficient 3.117; 95%CI 0.552-5.683; p=0.017) when compared with no SGLT2i use. This positive association persisted in the fully adjusted model (coefficient 3.108; 95%CI 0.274-5.943; p=0.032). ≥5 years SGLT2i use was also positively associated with increase in RBANS score in language (coefficient 3.786; 95%CI 0.287-7.284; p=0.034) in the fully adjusted analysis.

Lessons Learnt

SGLT2i potentially ameliorates the deleterious effect of T2DM on cognitive function, in particular immediate memory and language.

Conclusion

Our findings have revealed a previously unobserved association between long-term SGLT2i use and improved cognitive scores in immediate memory and language domains. This may pave the way for future studies on the role of SGLT2i in ameliorating cognitive decline in T2DM.

Additional Information

This project attained Gold (Category: SHBC Best Poster Award (Clinical Research)) at the Singapore Health & Biomedical Congress (SHBC) 2021

Project Category

Applied Research / Translational Research, Quantitative Research, Care Continuum, Chronic Care

Keywords

SGLT2i, Cognitive Function, Type 2 Diabetes Mellitus

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Association between long term use of sodium-glucose co-transporter-2 (SGLT2) inhibitors and cognitive function

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BACKGROUND

- Sodium-glucose co-transporter-2 inhibitor (SGLT2i) reduces risk of adverse cardiovascular and kidney events.[1]
- Recent studies in mice reported neuro-protective effects of SGLT2i.[2-3]
- There is no published study on the definitive neuro-protective effect of SGLT2i in humans,
- We aimed to explore longitudinal association between SGLT2i use and cognitive function in patients with Type 2 diabetes mellitus (T2DM).
- We hypothesize that use of SGLT2i is associated with improved cognitive function in T2DM.

METHODS

- Prospective cohort study of 428 patients from SMART2D cohort. See Fig 1.
- Cognition was assessed with Repeatable Battery for the Assessment of Neuropsychological Status(RBANS).[4] See Fig 2.
- Outcome was change in RBANS score calculated as follow-up score minus baseline score
- Multiple linear regression was performed, adjusting for demographics, education, clinical parameters, presence of APOE $_{\varepsilon}$4 allele, medications and follow-up period.

Fig 1
Study Population

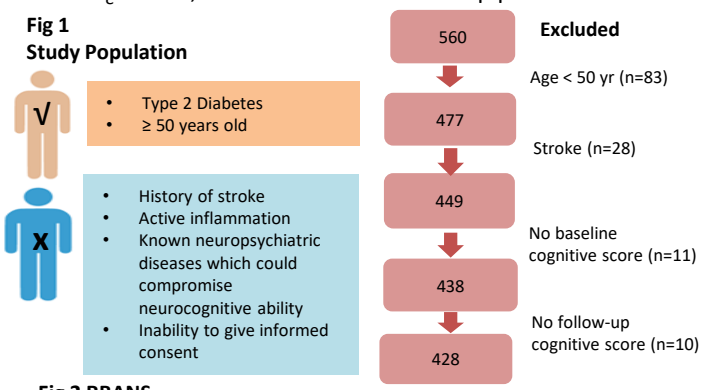
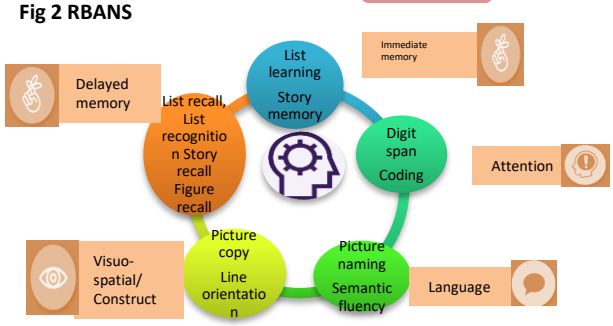


Fig 2 RBANS



RESULTS

- Baseline characteristics are shown in Table 1. There were 165 patients (38.6%) using SGLT2i – 115 (26.9%) for < 5 years and 50 (11.7%) for ≥ 5 years.
- Over a follow-up period of up to 6.4 years (median 4.6, IQR 4.1-5.0), RBANS total and all cognitive domains decreased in both groups (non-SGLT2i user and SGLT2i user), except for immediate memory and language for SGLT2i user.
- Compared to non-use of SGLT2i, use of SGLT2i was positively associated with increase of RBANS score in immediate memory in Model 1. The association was lost in Model 2. See Fig 3.
- Compared to non-use of SGLT2i, ≥ 5 years use of SGLT2i was associated with increased RBANS score in total score, immediate memory and language. This association persisted in Model 1 for total score, and in Models 1 and 2 for immediate memory and language. See Fig 4.

RESULTS (CONTINUED)

Table 1. Baseline characteristics stratified by use of SGLT2i

Variable	All	Use of SGLT2i		P-value
		No	Yes	
Number	428	263 (61.5)	165 (38.5)	
Age (years)	61.1 ± 6.8	62.5 ± 7.0	58.9 ± 6.0	<0.001
Male (%)	232 (54.2)	137 (52.1)	95 (57.6)	0.268
Education < 7yrs	101 (23.6)	68 (25.9)	33 (20.0)	0.165
DM duration (yrs)	15.6 ± 9.0	14.7 ± 9.2	17.1 ± 8.4	0.008
SBP (mmHg)	139.0 ± 16.6	140.2 ± 17.5	17.1 ± 8.4	0.052
HbA1c (%)	7.9 ± 1.6	7.5 ± 1.4	8.6 ± 1.7	<0.001
LDL-C (mmol/l)	2.6 ± 0.7	2.6 ± 0.7	2.6 ± 0.8	0.882
eGFR (ml/min/1.73m^2)	82.1 ± 29.0	80.5 ± 30.2	84.7 ± 26.8	0.143
uACR (mg/g)	21.8 (6.4-97.0)	18.0 (5.7-68.7)	34.7 (8.0-170.0)	0.005
Metformin use (%)	369 (86.2)	209 (79.5)	160 (97.0)	<0.001
Insulin use (%)	147 (34.4)	58 (22.1)	89 (54.3)	<0.001
APOE e4 allele (%)	58 (16.6)	33 (15.0)	25 (19.2)	0.304

Fig 3. Association between SGLT2i (vs none) and change RBANS score

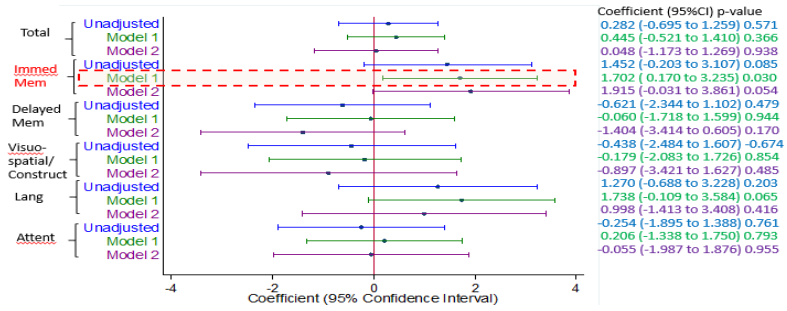
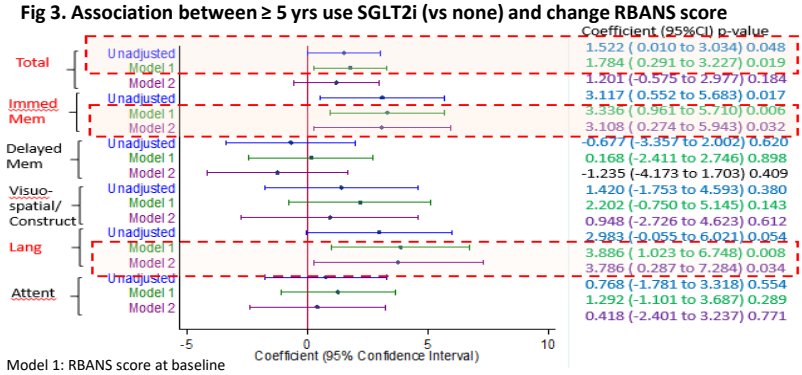


Fig 3. Association between ≥ 5 yrs use SGLT2i (vs none) and change RBANS score



Model 1: RBANS score at baseline
Model 2: Model 1+ age, gender, ethnicity, education, DM duration, HbA1c, SBP, eGFR, log-transformed uACR, metformin use, insulin use, APOE e4 allele and log-transformed duration of follow-up

CONCLUSIONS

- ≥ 5 years use of SGLT2i was independently associated with increased RBANS score, in particular in immediate memory and language (previously unobserved).
- Possible mechanism of action of SGLT2i include reduction of cerebral oxidative stress, inflammation[5], increase of brain-derived neurotrophic factor and amelioration of T2DM-induced ultrastructural remodeling of neurovascular unit and neuroglia[2].
- There is no current guidance on choice of anti-diabetic agent in ameliorating cognitive decline. Our findings may bring heightened awareness on potential neuro-protective benefits of SGLT2i.
- Our results may pave the way for future studies to understand exact mechanism underlying neuroprotective effect of SGLT2i.

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References: 1. DK MG, Shih WJ, Cosentino F et al. JAMA Cardiol 2020; 6: 148-58; 2. Hayden MR, Grant DG, Aroor AR et al. Brain Sci 2019; 9; 3. Hierro-Bujalance C, Infante-Garcia C, Del Marco A et al. Alzheimers Res Ther 2020; 12: 40; 4. Randolph C, Tierney MC, Chase TN. J Clin Exp Neuropsychol 1998;20:310e9; 5. Lin B, Koibuchi N, Hasegawa Y et al. Cardiovasc Diabetol 2014; 13: 148