Central-to-brachial blood pressure amplification in type 2 diabetes: a systematic review and meta-analysis

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Abstract

Due to systolic blood pressure (SBP) amplification, brachial SBP may not accurately reflect central SBP, the pressure the organs are exposed to. Patients with type 2 diabetes (T2D) have vascular irregularities that may affect blood pressure (BP) amplification and central BP indices (i.e. augmentation index [AIx] and augmentation pressure [AP]). By systematic review and meta-analysis, this study aimed firstly to determine the magnitude of central-to-brachial SBP and pulse pressure (PP) amplification in T2D compared to healthy controls and secondly, the difference in AIx and AP between the groups. Online databases were searched for published studies reporting invasive or non-invasive central and brachial SBP in T2D and healthy controls up to the 20th of February 2018. Random effects meta-analyses and meta-regression were used to analyse the studies.

18 studies (all non-invasive; 17 radial tonometry, 1 carotid tonometry, 2 brachial oscillometry) with a total of 2,758 patients with T2D and 10,561 healthy controls were identified. There was no significant difference in SBP amplification between groups (T2D=9.9±4.7, healthy controls=9.6±4.5 mmHg, p=0.84; pooled difference=0.64 mmHg, 95%CI -0.27 1.54, p=0.17) or PP amplification ratio (p=0.16). However, among these studies, central BP indices (AIx corrected for heart rate and AP) were significantly higher in T2D ($p<0.05$ for both). Despite a similar magnitude of central-to-brachial SBP amplification, patients with T2D have increased central systolic loading (AIx and AP) that cannot be discerned from brachial BP alone.

Introduction

High blood pressure (BP) is associated with adverse cardiovascular (CV) outcomes (1, 2). In clinical practice, BP is typically measured at the brachial artery by cuff (3); however, due to potential amplification in systolic BP (SBP), brachial SBP may not equal the pressure in the aorta (central SBP); the pressure to which the heart, brain and kidneys are exposed (4-6). Several methods are available to estimate central BP using non-invasive techniques (7). Indeed, recent meta-analysis of data from such techniques showed that central SBP had a significantly stronger relationship to target organ damage and increased CV disease risk, compared with brachial SBP (8). However, central SBP is influenced by a number of physiological factors. Specifically, among patients with type 2 diabetes mellitus (T2D), vascular irregularities (e.g. endothelial dysfunction (9), central (10-12) and peripheral (13) arterial stiffening) and increased CV disease risk factors (hyperlipidaemia (14) and smoking (15)) may have a greater influence on central rather than brachial SBP, culminating in higher central systolic stress. Thus, even taking into account that cuff brachial BP methods have variable accuracy (6), there may be particular inadequacy in capturing risk related to central BP in higher risk patients (16, 17), such as those with T2D. We have previously observed similar central-to-brachial SBP amplification in patients with T2D compared to healthy controls (18), but this has never been examined by systematic review and meta-analysis.

In patients with T2D, vascular dysfunction may alter the timing and direction of arterial pressure wave travel in the aorta (19, 20) and other large arteries. Waveform indices: augmentation pressure (AP); the difference between the second and first central systolic peaks, and augmentation index (AIx); AP expressed as a percentage of pulse pressure, are markers of this central systolic load that may be elevated in patients with

T2D (12, 21). Despite numerous studies examining AIx and AP in patients with T2D, it remains unclear as to whether these indices are systematically different compared to healthy individuals. The primary aim of this study was to determine the magnitude of central-to-brachial SBP and PP amplification in patients with T2D compared to apparently healthy controls and secondly, within the same dataset, to determine the difference in AIx and AP between the groups.

Materials and Methods

Literature search and methods. The search methods used in this study followed the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) (22) and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) (23) reporting guidelines. Two reviewers (RC and MS) independently conducted a literature search of six electronic databases (MEDLINE, CINAHL, Cochrane, EMBASE, Scopus and Web of Science) independently for studies reporting both central and brachial SBP in patients with T2D from inception up to the 20th of February 2018. The screening of titles, abstracts and full-texts were done independently by the two reviewers and then the results compared. The literature search was based on the MEDLINE search strategy (Appendix) and searches of other databases were adapted to meet the specific requirements of the database. Additionally, the reference lists of relevant original and review articles were also searched.

Criteria for study inclusion. Studies were included in the systematic review if they met the following criteria: 1) a full length publication in a peer-reviewed journal; 2) a human study involving adults >18 years of age; 3) reported central and brachial SBP and diastolic BP using invasive or non-invasive techniques; 4) central and brachial SBP were measured either simultaneously or consecutively and; 5) data were reported

separately for individuals with T2D and a control (apparently healthy) group. Since the criteria for study inclusion could be derived from different types of study designs (e.g. observational case-control, longitudinal or controlled trials), there was no restriction on this criteria. Studies for the meta-analyses of AIx and AP were only included if they met the inclusion criteria for the primary aim as above. The Newcastle-Ottawa Scale (24) was used to assess the quality of included studies. The Scale awards a maximum of nine stars across three categories; selection of study participants (4 stars), comparability between groups of participants (2 stars) and exposure (3 stars). A greater number of stars indicates a higher quality study.

Outcome measures. The primary outcome measure was the difference in central-to-brachial SBP amplification. Secondary outcomes were central-to-brachial PP amplification, AIx, (including AIx corrected for a heart rate of 75 beats per minute [bpm]) and AP. SBP amplification was determined as brachial SBP – central SBP, and was calculated from the average brachial SBP and central SBP if not reported within individual papers. PP amplification ratio was determined by brachial PP divided by central PP. If PP (brachial or central) was not reported, it was calculated as SBP – diastolic BP (for brachial (21, 25-28) and central (21, 29) BP). Where AIx was not reported but central PP and AP were available or calculated, AIx was calculated via equation 1 below, with standard deviations calculated by the Delta method (30). In some cases, AP could not be calculated due to insufficient availability of data within the individual studies.

Equation 1:

AIx = (Augmentation pressure/central PP) x 100

Data extraction. Two reviewers (RC and PO) extracted data from each eligible study independently. For the systematic review the following data were extracted from each individual paper; the characteristics of the study population (including the age, sex, body mass index [BMI], insulin levels, glycated hemoglobin [HbA1c], medications, disease status and duration of diabetes), central and brachial SBP and diastolic BP, central PP, brachial PP, AIx, AP, heart rate, statistical methods and method of determining central and brachial SBP and diastolic BP (table 1). The study by Maple Brown et al. (26) was performed in two distinct populations (indigenous Australians and Australians with European ancestry) in which data were presented for both a group with T2D and non-diabetic subgroup. Therefore, these populations were treated as separate studies.

Statistical analysis. Random effects analyses were performed comparing the difference in central-to-brachial SBP amplification and PP amplification ratio, AIx and AP between patients with T2D and apparently healthy controls. Five separate meta-analyses were performed and studies could be included in more than one meta-analysis if the appropriate data was reported or able to be calculated. Heterogeneity between studies was reported using the I^2 statistic and factors associated with heterogeneity were examined by performing meta-regression analyses to examine the effect of age, sex, BMI, heart rate, insulin levels, HbA1c, antihypertensive medication use and diabetes duration (in the diabetic group) on the difference in central-to-brachial SBP amplification between individuals with and without T2D.

Sensitivity analyses were performed to assess whether three studies (29, 31, 32) that used methods other than radial tonometry calibrated with SBP and diastolic BP to determine central SBP caused any difference in effect size. Sensitivity analyses were also performed to assess whether five studies (26, 29, 33-35) in which the age the

difference between T2D and controls was ≥10 years influenced the effect size. Three studies (21, 31, 36) reported variance as either interquartile range or 95% confidence intervals and were therefore, converted to standard deviations for analysis. In these studies, the mean or median was within the confidence intervals or interquartile range and, therefore, the data was assumed to be normally distributed. Two studies containing data from similar cohorts were included in separate analyses, one in the analysis of central-to-brachial SBP and PP amplification (33) and one in the analysis of AIx and AP (37). All data from each individual study was reported as unadjusted. Publication bias was assessed visually via funnel plots and with Eggers test for bias.

Results

Literature search and systematic review. A summary of the literature search procedure and results is shown in Figure 1. The original search of six online databases revealed 20,015 original articles of which 19,906 were excluded (due to being duplications or based on review of title or abstract or both), leaving 109 potentially relevant articles that required full text reviews. 90 of these were excluded (due to required data being unavailable, unable to extract T2D data, failing to include a control group or were conference abstracts/reports), leaving 19 articles for the final systematic review (table 1) and 18 for the primary meta-analysis (one study was excluded from the meta-analysis due to duplicate data).

Summary of studies included in meta-analysis. The 18 studies eligible for meta-analysis included a total of 2,758 patients with T2D and 10,561 healthy controls. Patients with T2D were older (57±5 vs 51±5 years, p=0.001), of greater BMI (29.9±1.5 vs 26.2±1.6 kg/m^2, p=<0.001) and were more likely to be male (55 vs 48%, p=0.16; table 1) compared to apparently healthy controls. The majority of the studies estimated central SBP using radial applanation tonometry and application of a generalized transfer

function, with only three (29, 31, 32) using alternate methods (carotid applanation tonometry, Mobil-o-graph and Arteriograph). Central and brachial SBP were elevated in patients with T2D compared to healthy controls (125±9 vs 115±11 mmHg, p=0.007 and 134±9 vs 125±9 mmHg, p=0.003 respectively).

Central-to-brachial SBP amplification. The pooled central-to-brachial SBP amplification data from all studies showed that there was minimal difference between patients with T2D and healthy controls (0.64 mmHg, 95%CI -0.27, 1.54, p=0.17; figure 2). The difference in age between individuals with and without T2D, did not explain the variance in the pooled central-to-brachial SBP amplification data (R^2 = 0%) nor did the difference in sex (R^2 = 0%), BMI (R^2 = 0%), heart rate (R^2 = 0%), or antihypertensive medication use (R^2 = 0%). However, the difference in HbA1c explained 50.9% (p=0.03) of the heterogeneity in the difference in central-to-brachial SBP amplification between those with (data available in n=872) and without T2D (n=732). Further, although non-significant, the duration of diabetes explained 16.3% (p=0.15) of the variance in central-to-brachial SBP amplification between the groups.

Removal of the five studies in which the age difference between patients with T2D and controls was $\geq$ 10 years, made little difference to the overall pooled result (1.06 mmHg, 95% CI -0.07, 2.18, p=0.067). Central SBP was estimated from the carotid artery rather than the aorta in the study by Chirinos et al. (31); however, removal of this study from the analysis made little difference to the overall pooled result (0.6 mmHg, 95%CI -0.3, 1.5, p=0.18). Furthermore, the removal of the three studies (29, 31, 32) that used alternate methods to determine central SBP other than radial tonometry, did not affect the overall pooled result (0.6 mmHg, 95%CI -0.5, 1.6, p=0.28). Stratification of the pooled difference between controls and T2D in central-to-brachial SBP amplification by quality, showed that in studies of low quality (scoring

<5 Newcastle-Ottawa Scale) there was little to no difference between groups (-0.06 mmHg, 95%CI: -1.42 , 1.30) while there was a difference between groups in higher quality studies (1.08 mmHg, 95%CI: 0.00, 2.17). However, the difference between low and high quality studies was not statistically significant (p=0.20).

Central-to-brachial PP amplification. There was no difference between patients with T2D and healthy controls in central-to-brachial PP amplification (-0.031, 95%CI -0.074, 0.012, p=0.16; figure 3A). Nor was there a difference in PP amplification when the five studies with large age differences between groups were removed (-0.02, 95%CI -0.06, 0.02, p=0.34). The mean PP amplification was 1.3±0.1 mmHg in patients with T2D, and was 1.3±0.1 mmHg in healthy controls.

Augmentation index and augmentation pressure. AIx was calculated using equation 1 in two studies (11, 21). However, insufficient data was provided to calculate AIx in six studies (18, 27, 29, 31, 36, 38) and AP in ten studies (11, 18, 27, 29, 31, 32, 35, 36, 38, 39), and therefore, these studies were excluded from this analysis. Data for AIx corrected for heart rate was only available in seven studies (27, 29, 36, 37, 39-41). All but one (32) study used radial applanation tonometry to measure AIx. Of those that did, the pooled data showed that AIx was elevated in patients with T2D compared to healthy controls (2.39%, 95% CI 0.18, 4.60, p=0.03; figure 3B), as was heart rate corrected AIx (4.34%, 95% CI 2.70, 5.97, p<0.001; figure 3C). When the study that used an alternate method to measure AIx (suprasystolic waveform analysis) was included in the analysis, the difference in AIx between those with and without T2D was borderline significant (1.98%, 95% CI -0.18, 4.15, p=0.07). However, removal of the five studies in which the age difference between patients with T2D and controls was $\geq$ 10 years, rendered the difference in AIx between groups non-significant (1.53%, 95% CI -0.50, 3.55, p=0.14), but not for heart rate corrected AIx (4.97%, 95% CI 2.93, 7.02, p<0.0001).

AP was significantly greater in patients with T2D compared to apparently healthy controls (2.93 mmHg, 95% CI 0.93, 4.93, p=0.004; figure 3D) and remained significant after removal of the studies where the age difference between groups was ≥ 10 years (1.87 mmHg, 95% CI 0.39, 3.35, p=0.01).

Publication bias. Funnel plots (figure 4) and Egger's test indicated that there was relatively little influence of any publication bias.

Discussion

The main findings of this study were; 1) no significant difference in central-to-brachial SBP amplification or PP amplification ratio between patients with and without T2D; 2) markers of central systolic load (AIx and AP) were significantly increased in patients with T2D compared to apparently healthy controls and; 3) both brachial and central SBP were significantly elevated in patients with T2D compared to controls. Taken together, these findings suggest that despite no difference in SBP amplification or PP amplification ratio compared to healthy controls, patients with T2D have increased central systolic load, which cannot be identified based on a traditional brachial cuff BP measures alone.

Central BP and markers of central systolic load have been shown to be elevated in populations at increased CV disease risk compared to controls, despite having similar brachial BP (11, 14, 41-44). In a large cohort of individuals from the Anglo-Cardiff Collaborative Trial, McEniery et al. (34) reported that diabetes was more strongly associated with higher central PP relative to brachial PP than other CV risk factors including hypertension, hypercholesterolemia and smoking. The discrepancy between central and brachial SBP is purported to be influenced by numerous demographic or physiological factors including age, sex, body mass index and heart rate (45-47).

Different classes of antihypertensive medications can also elicit substantial variability in SBP amplification (48, 49). Yet in our analysis, none of these potentially influential factors significantly explained the variance in SBP amplification among the study populations.

The difference in mean HbA1c between individuals with and without T2D explained a large part of the heterogeneity observed in the central-to-brachial SBP amplification. However, this finding should be interpreted with caution due to the small amount of data available on HbA1c. Nonetheless, given that hyperglyceamia (known to be related to increased arterial stiffness) was well controlled in some patients with T2D (26, 29, 31) compared to others (25, 26, 28), we speculate there may have been differing degrees of arterial stiffening that could have influenced central-to-brachial SBP amplification between the studies included in the meta-analysis. Further, in patients with T2D, long term exposure to CV risk factors (hyperglycaemia (50), advanced glycation end products (51)), and the duration of diabetes (52) itself, contributes to aortic stiffness (42) via adverse changes in the elastin/collagen composition of the arterial wall (53). Hashimoto and Ito (54) hypothesized that this increase in aortic stiffness may disrupt blood flow patterns in the proximal aorta (55), exaggerate diastolic flow reversal (54) and elevate central AIx, AP and SBP. Smaller aortic root diameter, may be an additional factor further augmenting central systolic load among patients with T2D (56). Our findings support these data relating to raised AIx, AP and central SBP among patients with T2D, but the concomitant increase in brachial SBP meant there was no difference in the level of central-to-brachial SBP and PP amplification compared to healthy controls. Similarly, some of our previous work (18), implies that an individual's level of central-to-brachial SBP amplification may be relatively fixed irrespective of BP level.

Most of the studies included in the meta-analysis estimated central SBP from radial pressure waveforms acquired by tonometry (calibrated with brachial SBP and diastolic BP) and a generalized transfer function. This approach assumes there is no SBP amplification from the brachial to radial arteries. However, significant SBP amplification in this arterial segment has been demonstrated among healthy individuals (57) as well as patients with T2D, albeit to a lesser degree in the latter (14 ± 7 vs 9 ± 8 mmHg, p=0.042) (58). Failure to account for this additional SBP amplification may introduce error into estimation of central SBP (and thus, the level of SBP amplification), the magnitude of which could differ between healthy individuals and those with T2D. Another source of error among the studies examined was the use of cuff BP to calibrate waveforms, as this method has variable accuracy for determining either brachial or aortic (intra-arterial) BP (6). Lastly, diabetic-specific transfer functions to estimate central SBP may produce more accurate estimations of central SBP (59). Importantly, none of these limitations will affect AIx as a pressure independent variable. Nonetheless, more accurate non-invasive measurement of both brachial and central BP is needed to understand the true level of central-to-brachial SBP amplification in patients with T2D and healthy controls (60).

Limitations. Although reviews and reference lists of included studies were searched for additional studies, we did not search for ongoing studies or grey literature, nor were study authors contacted and thus some data may have been missed. That said, the majority of the 37 studies with missing data focused on markers other than central SBP (i.e. augmentation index) as the main outcome variable and, therefore, this limitation may not have substantially influenced the findings.

Summary and conclusions. This is the first systematic review and meta-analysis to compare central-to-brachial SBP and PP amplification ratio, AIx and AP between

patients with T2D and apparently healthy controls. According to conventional methods to assess these parameters, our data showed that there was no difference in central-to-brachial SBP or PP amplification between the groups, despite elevated markers of central systolic load in patients with T2D. Our findings suggest that in patients with T2D, risk related to BP may not be adequately captured via a measurement of either brachial or central SBP alone and that pressure-independent parameters such as AIx may be a useful addition.

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Conflicts of interest: None.

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Figure legends.

Figure 1. Summary of literature search and selection procedure for articles included in the systematic review and meta-analysis. BP, blood pressure; T2D, type 2 diabetes mellitus.

Figure 2. Pooled estimates and 95% confidence intervals for amplification in central to brachial systolic blood pressure (SBP) in patients with type 2 diabetes mellitus (T2D) compared to healthy individuals. I^2=87.3% p=0.17. The forest plot indicates that central-to-brachial SBP amplification was slightly, although not significantly, higher in patients with T2D.

Figure 3. Pooled estimates and 95% confidence intervals for; (A) Amplification in central to brachial pulse pressure, I^2=96.4% p=0.15; (B) augmentation index, I^2=90.8% p=0.03; (C) augmentation index adjusted for a heart rate of 75 beats per minute (bpm), I^2=61.0% p<0.001; (D) augmentation pressure, I^2=91.7% p=0.004

Figure 4. Funnel plots representing the publication bias for individual studies for each meta-analysis. (A) Central to brachial systolic blood pressure amplification; (B) central to brachial pulse pressure amplification; (C) augmentation index; (D) augmentation index corrected of heart rate of 75 beats per minute; (E) augmentation pressure. The results depict the relative absence of any publication bias.