Adhesive capsulitis of the shoulder and diabetes: a meta-analysis of prevalence

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Summary

Background: **adhesive capsulitis (AC) results in progressive painful restriction in range of movement and can reduce function and quality of life. Whilst it has been associated with diabetes mellitus (DM), there is considerable variation in the reported prevalence of AC in the diabetic population. The aim of this study is to determine through meta-analysis the prevalence of AC in DM and examine whether it is influenced by type of DM or insulin therapy. We also aim to further establish the prevalence of DM in patients presenting with AC.**
Methods: **we conducted a literature search for terms regarding AC and DM on Embase and Pubmed NCBI.**
Results: **of 5411 articles identified, 18 were selected. Meta-analysis showed that patients with DM were 5 (95% CI 3.2-7.7) times more likely than controls to have AC. The overall prevalence of AC in DM was estimated at 13.4% (95% CI 10.2-17.2%). Comparison of prevalence in patients on insulin *vs* other treatments showed no significant difference between the two. Meta-analysis estimated the prevalence of DM in AC at 30% (95% CI 24-37%).**
Conclusion: **to our knowledge this is the first meta-analysis to estimate the overall prevalence of diabetes in a population with AC. A high prevalence of AC exists in DM and equally a high prevalence of DM is present in AC. Screening for DM should be considered in patients presenting with AC.**

KEY WORDS: idiopathic adhesive capsulitis, frozen shoulder, diabetes, prevalence.

Level of Evidence: Level III (meta-analysis).

Introduction

Adhesive capsulitis (AC) is a self-limiting condition. Patients typically present with an atraumatic history of progressive painful restriction in range of movement of the gleno-humeral joint. They exhibit a capsular pattern of restriction with external rotation being the most restricted followed by abduction in the plane of the scapula and then flexion. Codman in 1934 described a diagnostic criterion comprising of idiopathic onset, painful restriction of all gleno-humeral movements with limitation of flexion and external rotation with a normal radiograph[1,2].
AC is more common in women with a peak age of onset of 56 years[3,4]. It can have a variable duration but usually lasting between 1-3 years[3-5] without intervention, and can impact on patients' activities of daily living and reduce quality of life. Resolution may range from complete to varying degrees of limitation in shoulder movement.
Management of AC may be operative or non-operative, though the best management option remains controversial[6]. In a survey of upper limb orthopaedic surgeons in the United Kingdom, those preferring non-operative management favoured physiotherapy, whereas those preferring operative intervention favoured arthroscopic arthrolysis. Preference of management was largely based on surgeon experience and training as opposed to strong scientific evidence[7].
Although the aetiology of AC remains unknown, several risk factors are associated with this condition. These include previous trauma, increasing age, female gender, dyslipidaemia, hypertension, thyroid dysfunction and diabetes mellitus (DM)[8-15]. Sung et al. in 2014[16] found a statistically significant association of idiopath-

ic AC with hypercholesterolaemia and inflammatory lipoproteinaemias, though it was not possible to establish a cause-effect relationship.

The prevalence of AC in the general population is classically quoted as 2%, though it has been suggested that the real figure is closer to 0.75%[17]. However AC has a more variable prevalence in the diabetic population, in the reported literature.

Understanding prevalence rates of AC in DM, and DM in AC is important in guiding physicians and surgeons managing these conditions. It may guide research studies evaluating interventions in AC as to the inclusion of diabetic patients so as to reduce the risk of bias. Furthermore understanding the relationship between AC and DM may provide insights into the pathogenesis of AC.

In this study we review the available published literature, to estimate the prevalence of AC in DM and determine whether rates are influenced by DM type and treatment. We also aim to identify the prevalence of DM in AC.

Methodology

We conducted a literature search on 12th February 2014 using Embase and Pubmed NCBI (National Centre of Biotechnology Information). The search terms used were 'frozen shoulder,' 'adhesive capsulitis AND shoulder'. In the search, there were no re-

Table 1. Summary of studies identifying AC in populations with DM.

Study	Population	N	Prevalence
Kidwai et al. 2013[20]	India	413 210 T2DM 203 Controls	11% (in DM) p=0.001 (T2DM *vs* Controls)
Attar 2012[21]	Jeddah, Saudi Arabia	252	6.70%
Mathew et al. 2011[22]	India	310	16.45%
Ray et al. 2011[23]	Calcutta, India	100	18%
Dehghan et al. 2010[24]	Yazd, Iran	510 150 DM	13.30% (in DM)
Gupta et al. 2008[25]	Udupi, India	233	29.61%
Aydeniz et al. 2008[26]	Turkey	203 102 T2DM 101 non-DM	14.7 (in DM) p=0.009 (T2DM *vs* non-DM)
Thomas et al. 2007[27]	Scotland	1067 865 DM 202 non-DM	4.4% p=0.005
Sarkar et al. 2003[28]	Kolkata, India	1660 860 DM 800 non-DM	17.9 (in DM) p<0.001 (DM *vs* non-DM)
Cagliero et al. 2002[29]	Massachusetts	300	12% (DM *vs* non-DM)
Arkkila et al. 1996[30]	Finland	425	14% Overall 10% T1DM 22% T2DM
Pal et al. 1986[31]	Newcastle, UK	184 109 DM 75 non-DM	19% (in DM)
Bridgman 1972[32]	London, UK	1400 800 DM 600 non-DM	10.8% (in DM) p<0.005 (DM *vs* non-DM)

Table 2. Summary of studies identifying DM in populations with AC.

Study	Population	N	Prevalence (Event Rate)
Wang et al. 2013[33]	Australia	263 87 with AC	20% (in AC) p=0.005 (AC *vs* non-AC)
Tighe and Oakley 2008[34]	USA	88	38.6%
Milgrom et al. 2008[14]	Israel	224	29%
Rauoof et al. 2004[5]	Kashmir, India	100	27%
Withrington et al. 1985[35]	London, UK	60	40%

strictions on date of publication or language. Ethical approval was not required as there was no handling of confidential data. The study was conducted and meets the ethical standards as per the recommendations set out by Padulo et al. (2013)[18].
The search returned 5411 articles. The titles and abstracts of these were reviewed to identify those for full review. Studies were included if they identified prevalence of AC in a diabetic population or DM in a population with AC. Studies were excluded if the diagnosis of AC was not idiopathic i.e. it was related to trauma or post-operative. Case reports, duplicated data, incidence studies, reviews and opinion articles were also excluded. The studies had to define their understanding of AC.

Statistical analysis

A random-effects model was used to perform meta-analysis. Confidence intervals (95%) and summary risk ratios were calculated. Heterogeneity was assessed using tau^2, I^2, Q and p values. The level of significance was fixed at $p<0.05$. The data was analysed using Comprehensive meta-analysis version 2 (Biostat; Englewood, New Jersey, USA).

Results

Our initial search identified 5411 articles of which 18 were included for analysis (Fig. 1). Table 1 identifies the prevalence of AC in diabetes and Table 2 demonstrates the prevalence of DM in AC.

Meta-analysis

Thirteen studies examined the prevalence of AC in DM and meta-analysis showed an overall prevalence of AC in diabetes of 13.4% (95% CI 10.2-17.2%, Q=130.4, df12, $p<0.001$, $I^2=90.8$, $tau^2=0.27$) (Fig. 2). Funnel plot analysis did not show an obvious small study effect (Fig. 3).
Three studies compared AC prevalence in patients with T1DM and T2DM. Meta-analysis of AC prevalence showed no significant difference between T1DM and T2DM (5.8%, 95% CI 1.2-24.5 *vs* 12.4 95% CI 3-38.9, Q=0.5, p=0.47) (Fig. 4).
Two older studies compared AC prevalence in populations designated as having IDDM and NIDDM. Meta-analysis of AC prevalence showed no significant difference between IDDM and NIDDM (18.2%, 95% CI 10.6-29.3 *vs.* 11.8, 95% CI 6.9-19.6, Q=1.3, p=0.26) (Fig. 5). Similarly, meta-analysis of AC prevalence in patients on insulin treatment compared to NIDDM showed no significant difference (13.5%, 95% CI 8.3-21.3 *vs.* 12.3, 95% CI 5.9-23.6, Q=0.05, p=0.8) (Fig. 6).
Five studies compared AC prevalence in patients with DM compared to controls. The study by Sarkar et al. (2003)[28] used patients attending a rheumatology clinic as controls and as many rheumatological conditions can produce shoulder pathology that may be mistaken for AC, we excluded this study from the analysis. Meta-analysis showed that patients with DM were five times more likely than controls (95% CI 3.2-7.7, $p<0.001$) to have AC (Fig. 7).
Five studies assessed the prevalence of DM in a population with AC and meta-analysis showed that the prevalence of diabetes in this population was 30% (95% CI 24-37%, Q=10.4, df4, p=0.034, $I^2=61.6$, $tau^2=0.08$) (Fig. 8). Funnel plot analysis did not show an obvious small study effect (Fig. 9).

Discussion

Our meta-analysis demonstrates an overall mean prevalence of AC in DM of 13.4%. Conversely, the mean prevalence of DM in a population with AC was 30%. To our knowledge this is the first meta-analysis to estimate the overall prevalence of DM in a population with AC. In addition, we show that diabetic patients are 5 times more likely to develop AC compared to non-diabetic controls. Our analysis found no significant difference in the prevalence of AC between patients with T1DM and T2DM and also between patients on insulin therapy compared to oral hypoglycaemic agents. Yian et al. (2012)[36] have previously shown no relationship between the prevalence of AC and glycaemic control.
AC is considered more severe and resistant to treatment in the diabetic population[3,28,37]. In a recent study evaluating the outcomes of arthroscopic release in patients with AC, whilst 90% had excellent or good outcomes, the 10% who had fair outcomes, all had T1DM[38]. Indeed, in a separate study, DM was associated with a worse modified Constant score and range of shoulder movements post arthroscopic release for AC[39]. However, DM was not shown to be associated with a worse outcome following arthrographic distension for AC[40].
The underlying reasons in patients with DM for potentially worse outcomes and prolonged course in AC are complex. Boivin et al.[41] looked at the properties of the Achilles tendon of diabetic mice. They identified a significant increase in tendon diameter, and significant decreases in stiffness and elastic modulus in tendons from diabetic mice compared to controls, suggesting that altered tissue properties may account for the observed resistance of diabetics to treatment. In addition, a consequence of visceral adiposity in DM is inflammation that occurs via several inflammatory mediators[42,43]. Adipocytes secrete proteins and cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) resulting in overproduction of other pro-inflammatory cytokines, which in turn exacerbate inflammation. Adipocytes also release excess IL-13, which has been shown to result in hepatic fibrosis in mouse models[44] and may thus contribute to synovial and connective tissue fibrosis. Chronic inflammation can lead to excessive accumulation of

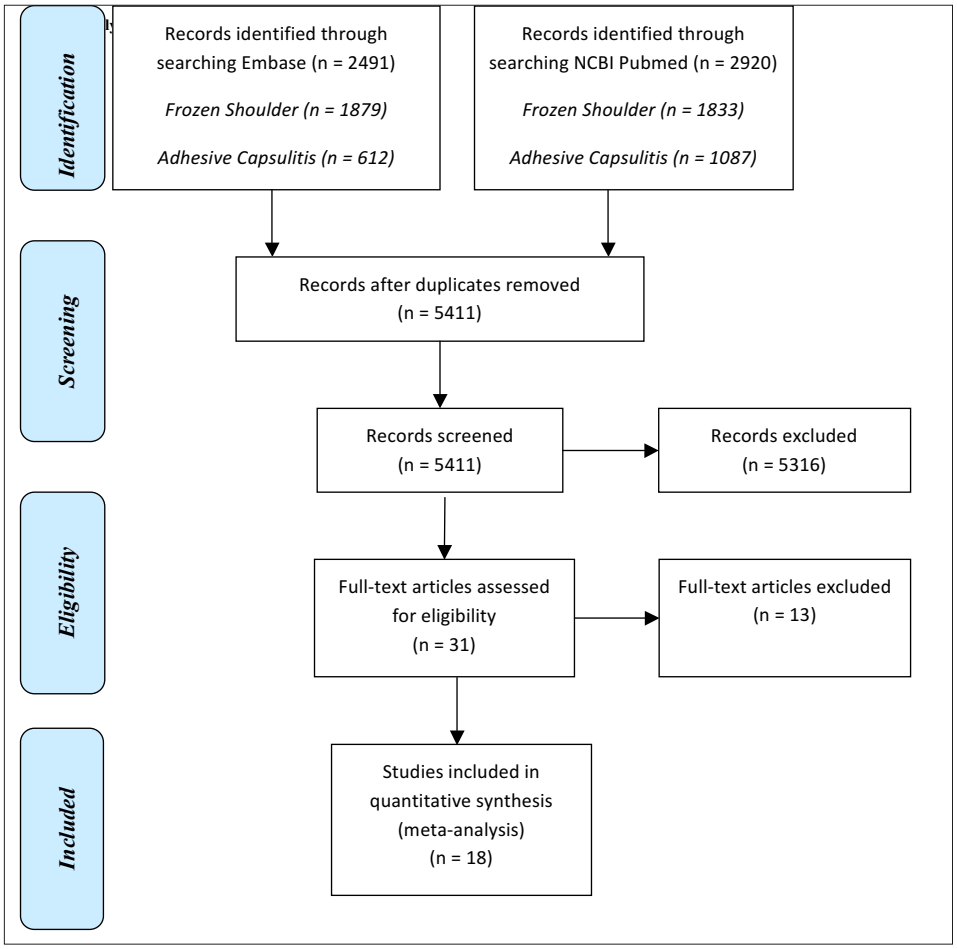

Figure 1. Literature search results (*PRISMA flowchart 2009*)[19].

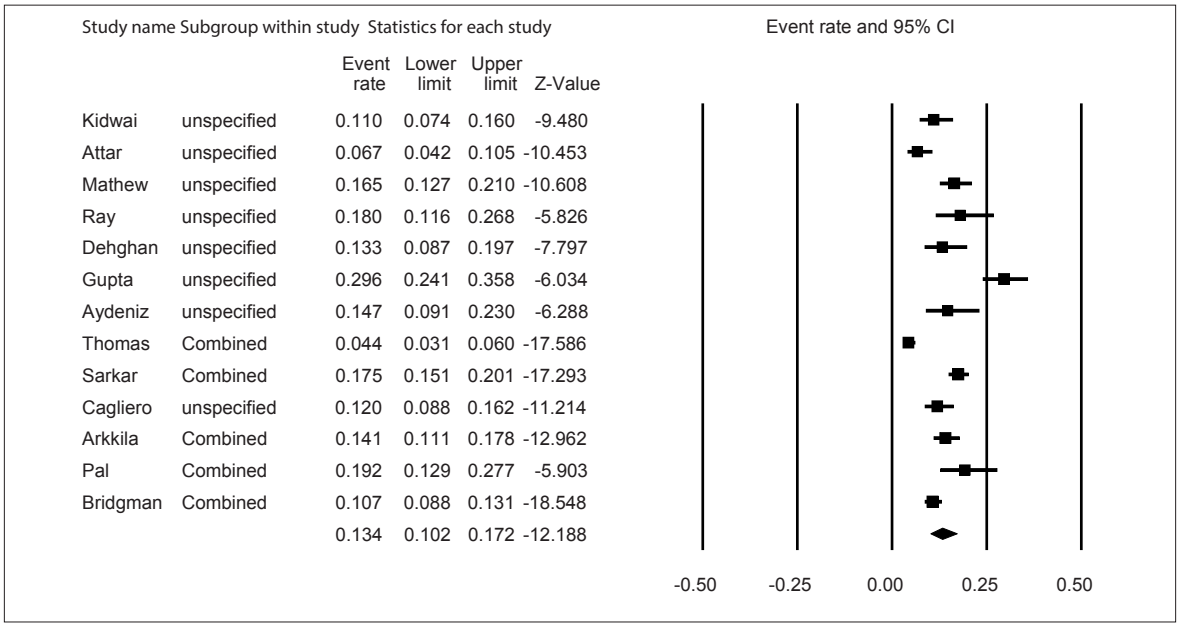

Figure 2. Meta-analysis of prevalence of AC in populations with DM. The 'subgroup within study' defines whether the study population was combined (T1DM and T2DM) or unspecified.

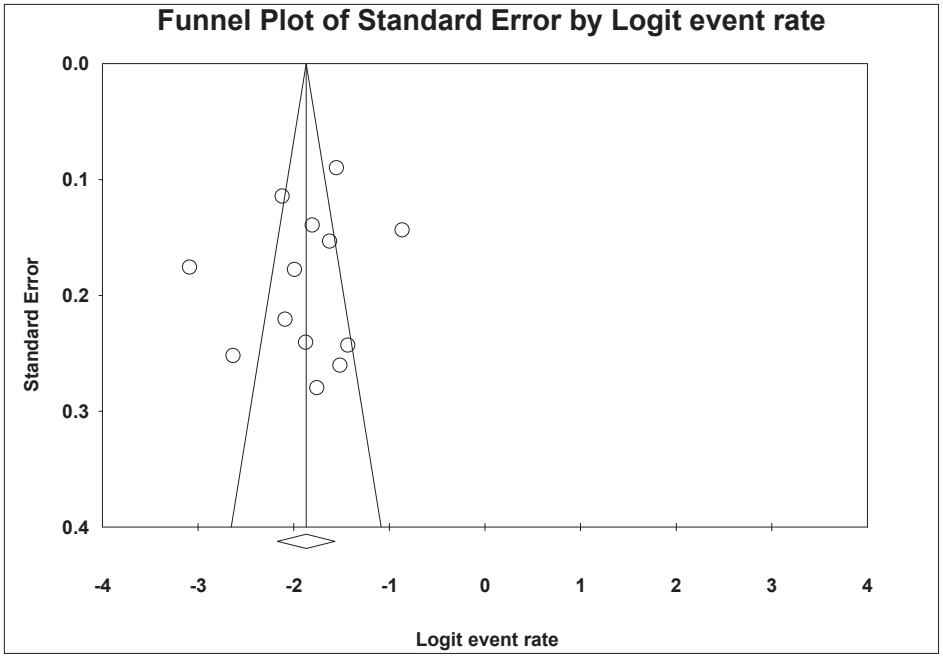

Figure 3. Funnel plot of prevalence of AC in populations with DM.

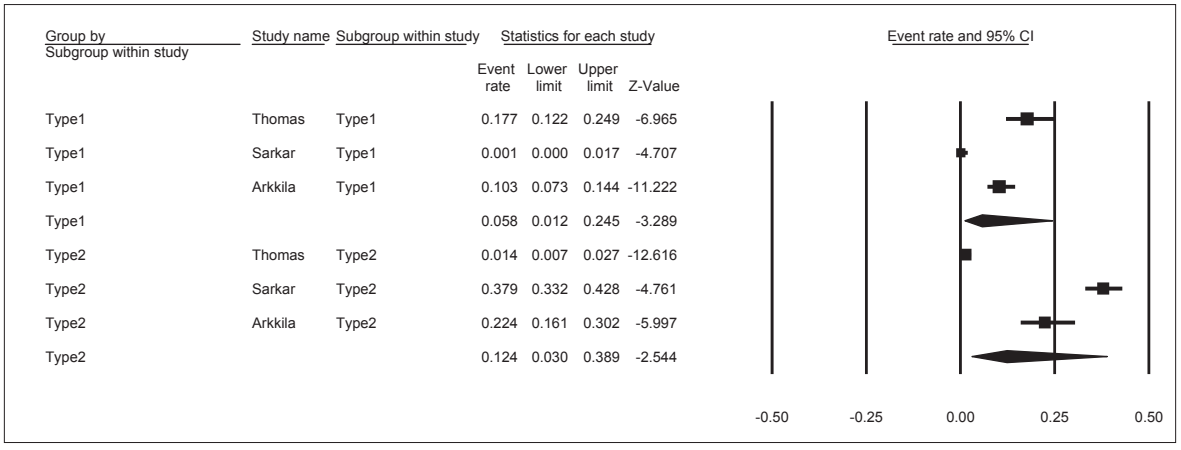

Figure 4. Meta-analysis of prevalence of AC in patients with T1DM and T2DM.

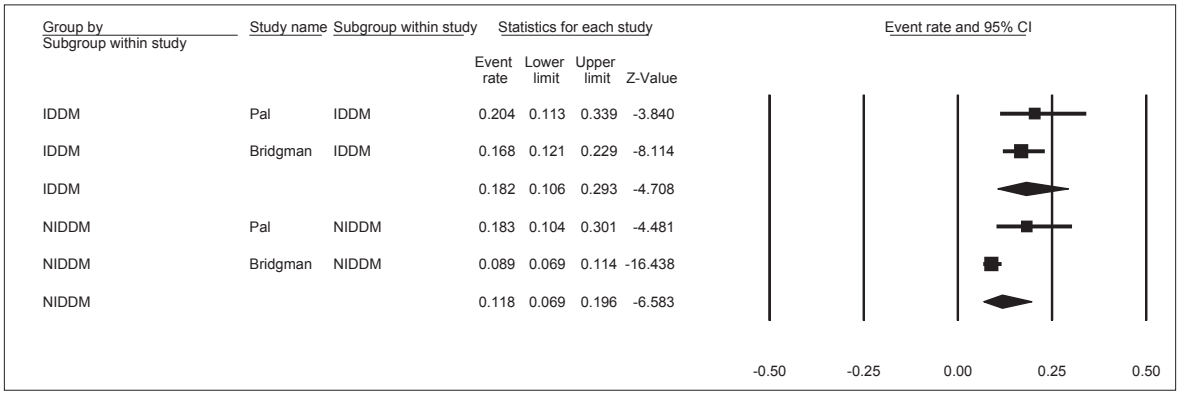

Figure 5. Meta-analysis of prevalence of AC in populations with IDDM and NIDDM.

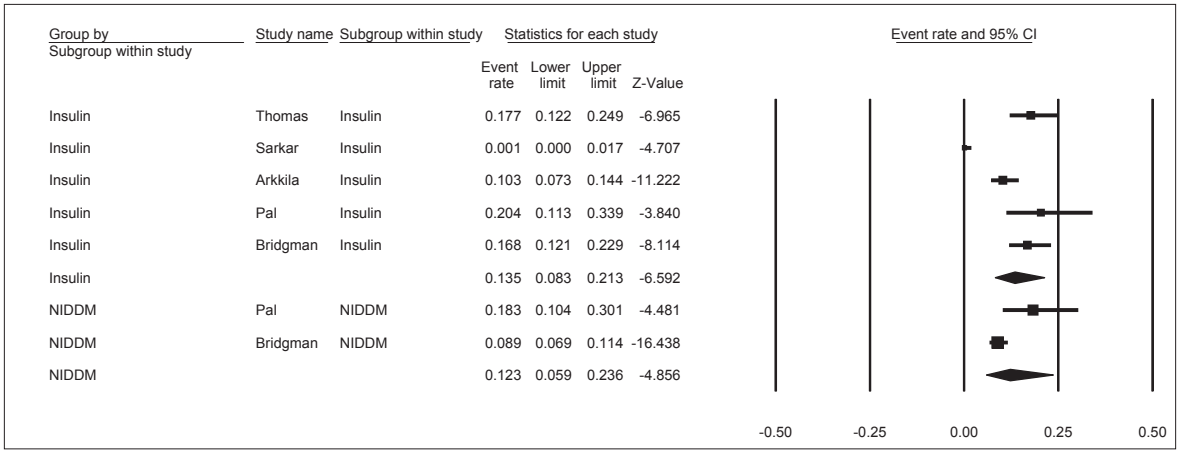

Figure 6. Meta-analysis of prevalence of AC in patients with DM on insulin therapy *versus* oral hypoglycaemic agents.

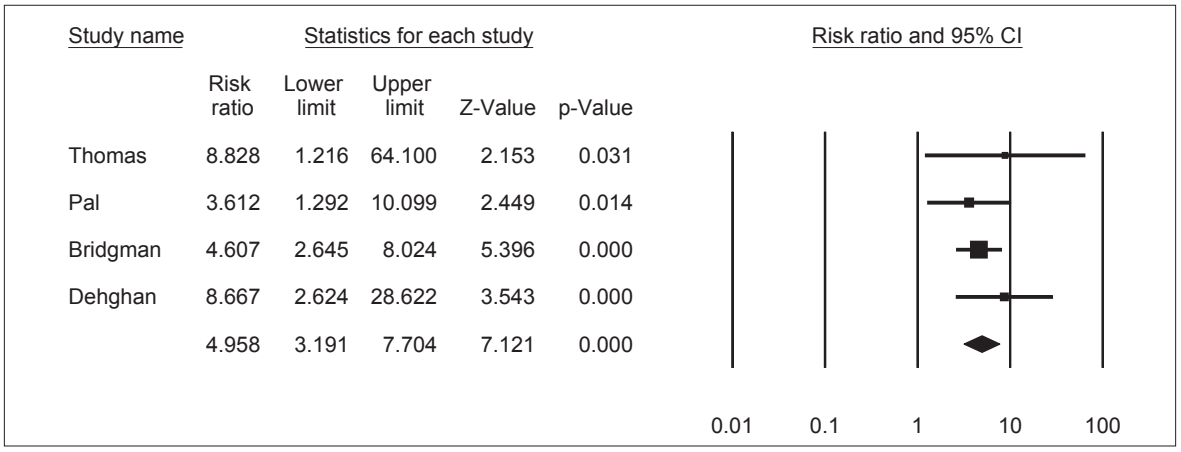

Figure 7. Meta-analysis of prevalence of AC in patients with DM *versus* non-diabetic controls.

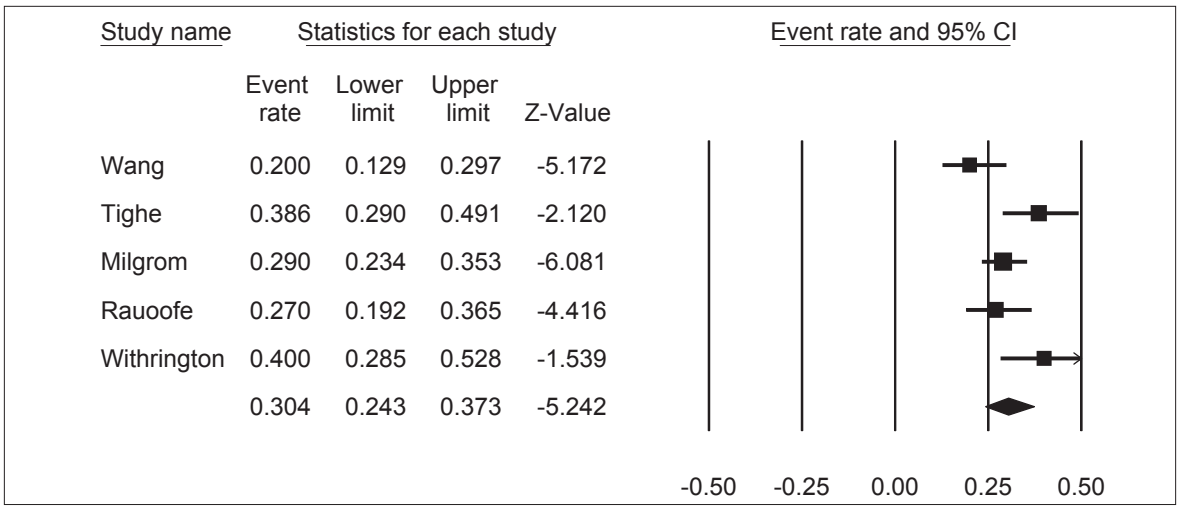

Figure 8. Meta-analysis of prevalence of DM in populations presenting with AC.

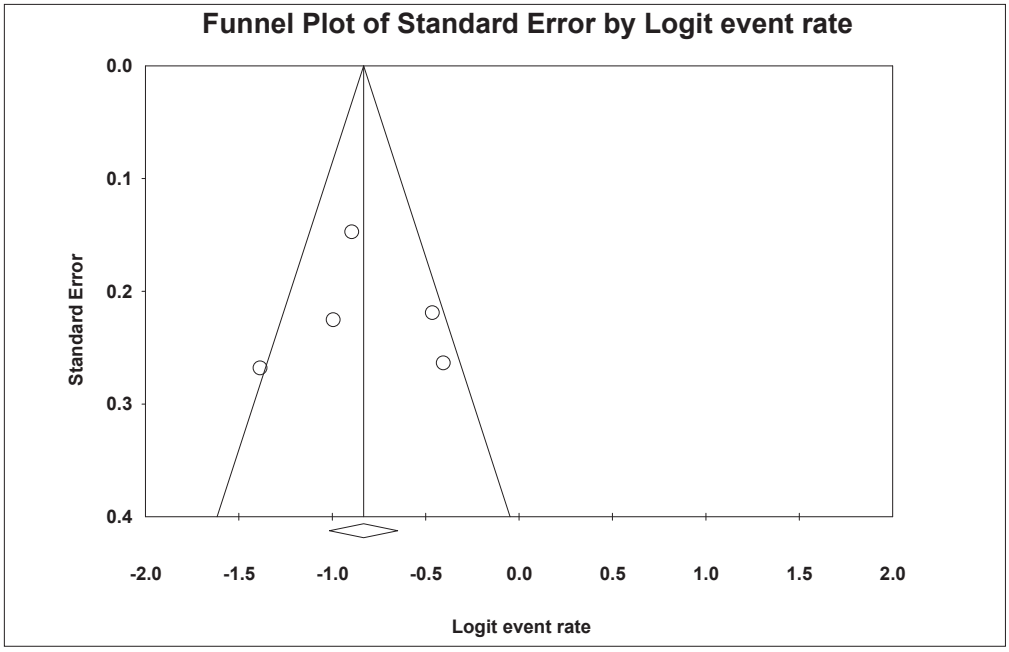

Figure 9. Funnel plot of prevalence of DM in populations presenting with AC.

collagen and other extracellular matrix components, which may result in destruction of normal tissue architecture[45]. Production of free fatty acids (FFAs) from adipocytes also leads to up-regulation of pro-inflammatory mediators and thus overproduction of inflammatory cytokines[43,46,47]. FFAs may also promote neutrophil survival and cause defective efferocytosis[43]. Neutrophils secrete TNF-α and IL-6, which may result in insulin resistance. Resultant hyperglycaemia interferes with the inflammatory cascade and inhibits phagocytosis of bacteria and apoptotic cells[43,48]. The combination of these factors could result in persistence of inflammation and limited disease resolution. AC is considered to be an inflammatory and fibrotic condition[49]. In the early stages of AC synovial and capsular fibrosis may occur as a result of inflammation and hypervascular synovial proliferation,[49,50] in part driven by increased expression of synovial vascular endothelial growth factor[2,6]. Up-regulation of inflammatory mediators in the capsule have also been demonstrated[44,49,51,52]. A study by Cho et al.[50] demonstrated that acid sensing ion channels may play a role in the pathogenesis of AC by mediating inflammatory pain.

Snedeker and Gautieri[52] reviewed collagen crosslinks in DM. They suggested that an increase in connective tissue stiffness in DM maybe linked to non-enzymatic oxidative reactions between glucose and collagen resulting in the formation of advanced glycation end-products[53-55]. Furthermore, in a recent review of hormones and tendinopathies, Oliva et al.[55] concurred that advanced glycation end-products result in changes in the microstructural organization of collagen fibres[56,57]. Alterations in the ultrastructure of collagen may thus result in changes in the biomechanical properties of tendons.

Our findings have important implications for clinical practice. They confirm the high prevalence and increased relative risk of AC in DM. This should increase the awareness of primary care providers and diabetologists to consider AC in patients presenting with shoulder symptoms. Earlier diagnosis with prompt referral and treatment may prevent progression to chronic, treatment resistant AC. In addition, rheumatologists and orthopaedic surgeons assessing patients with AC should enquire about a history of DM and if such a history is absent they should consider undertaking an assessment of HbA1c. The latter test is a simple blood test, which can enable patients to be stratified into those with normal glucose tolerance (HbA1c <5.7%), pre-diabetes (5.7-6.4%) and T2DM (HbA1c ≥ 6.5%)[58].

Limitations

We acknowledge a limitation of our analysis was that only four studies compared patients with DM to control subjects and the majority of the studies did not assess the type of DM. Furthermore, several earlier studies made reference to IDDM and NIDDM, terms that are now obsolete. Despite this, our meta-analysis has allowed us to estimate the overall prevalence of AC in DM and DM in AC from the currently available literature. It also provides an impetus to undertake more detailed and larger analyses if we are to better manage this debilitating condition.

Conclusion

In conclusion, diabetologists, rheumatologists and orthopaedic surgeons should be aware of the high

prevalence of DM in patients with AC and vice versa. Future studies assessing outcomes of interventions for AC should consider stratifying subjects into those with normal glucose tolerance, impaired glucose tolerance and T2DM based on HbA1c. This would provide meaningful insights into the effects of dysglycaemia and overall glycaemic control in relation to the development and outcomes of AC.

List of abbreviations:
CI – confidence interval
df – degrees of freedom
DM – diabetes mellitus
FFA – free fatty acid
HbA1c – haemoglobin A1c
IAC – idiopathic adhesive capsulitis
IDDM – insulin dependent diabetes mellitus
IL – interleukin
N (or n) – number
NCBI – National Centre of Biotechnology Information
NIDDM – non-insulin dependent diabetes mellitus
SD – standard deviation
TNF – tumour necrosis factor
T1DM – type 1 diabetes mellitus
T2DM – type 2 diabetes mellitus

Conflict of interests

The Authors declare that they have no conflict of interests regarding the publication of this paper.

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