The outcome of sternum healing among diabetic patients

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REVIEW
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The outcome of sternum healing among diabetic patients undergoing open heart surgery: a literature review

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ABSTRACT

Background: As part of the surgery, sternotomy is a common technique to expose the underlying organs, allowing surgeons to explore the targeted organ. Despite the benefits offered, it has several considerable complications; one of them is wound healing defect. The impairment of sternal wound healing after sternotomy could be superficial and/or deep. This condition is influenced by many factors, including diabetes mellitus, obesity, and other comorbidities. These anomalies will affect the normal healing process of the bone and other connective tissue, particularly after a major invasive event, such as in sternotomy. This study aimed to review the outcome of sternum healing among diabetics that underwent heart surgery with a sternotomy approach.
Methods: Works of literature reviewed in this study were obtained from Pubmed and Google Scholar databases starting from 1992 until April 2022. The keywords used were 'sternal wound healing', 'cardiac surgery', and 'diabetes mellitus'. An advanced search based on the exact phrases was conducted on Google Scholar. Gathered kinds of literature were then selected based on relevancy.
Results: The majority of articles reviewed were observational, and most of them had CABG as a part of open heart surgery, followed by valvular and aortic surgeries and others. The incidence of impaired sternal healing and other complications (superficial and/or deep) was more commonly seen among patients with diabetes. Most studies also reported a significant correlation between DM and the incidence of impaired sternal healing, suggesting that DM was a significant predictor of it.
Conclusion: Diabetes mellitus is a medical condition that must be taken into account among the candidates for open heart surgery, particularly if it is poorly controlled. The Hyperglycaemic state experienced by the patients will lead to multiorgan damage and immunological dysfunction that could affect the healing process of the sternum.

Keywords: *cardiac surgery, diabetes mellitus, sternal wound healing.*
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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease that is characterized by the elevation of blood glucose levels, also referred to as hyperglycemia. World Health Organization (WHO) stated in 2014, approximately 422 million people around the globe had diabetes mellitus; and in 2012, nearly 1.5 million people died due to this debilitating disease.[1] According to American Diabetes Association (ADA), diabetes mellitus can be classified into several groups based on the etiology, which are as follows: type I, type II, and gestational.[2] There is a significant association between diabetes with cardiovascular disease manifestation.[3] Among the other comorbidities associated with diabetes, atherosclerosis is a significant cause of mortality in humans, particularly if it occurs within the coronary vessels, because this could result in myocardial infarction – the leading cause of death worldwide.[4,5] Irreversibility of atherosclerosis and the need for adequate, continuous perfusion to the myocardial tissue made several attempts created to get rid of this problem. One of them is coronary artery bypass graft (CABG), by which the occluded vessel is bypassed by the new vessel in order to improve myocardial perfusion and viability, hence, reducing the incidence of myocardial infarction in the future.[6] CABG requires sternotomy – a procedure to cut and 'damage' the sternum, which must be done to allow the surgeons to explore the underlying structures. A sternotomy is a standard approach performed in almost every surgical procedure on the heart and mediastinum.[7] Sternotomy is also indicated in heart transplantation, valvular reconstruction, and pulmonary surgeries.[8,9] Immunological dysregulation and microangiopathy are the other comorbidities associated with the hyperglycemic state, and these conditions can impair cellular regeneration and vascular perfusion to the periphery sites, such as in wound healing after surgery. It has long been known that adequate oxygenation and nutrient supply to the site of injury are needed to achieve optimal healing and tissue renewal; otherwise, it could be halted, and several disorders could ensue, for example, in the case of malunion, osteonecrosis, and wound

dehiscence.[10] Considering the explanations above, this review aimed to describe the outcome of sternal healing among diabetic patients undergoing cardiac/other opened chest surgery.

METHODS

The pieces of literature reviewed in this study were obtained from PubMed and Google Scholar databases, with the publication years starting from 1992 – 2022. The advanced search was applied in Google Scholar with; all of the words: 'sternal healing after cardiac surgery among diabetic patients'; exact phrase: 'sternal healing'; and at least one word: 'diabetes mellitus'. These words were meant to be included anywhere in the article. The advanced search was not done on PubMed, with the keywords used: 'sternal wound healing', 'cardiac surgery', and 'diabetes mellitus'. This strategy resulted in 44 and 252 kinds of literature shown from PubMed and Google Scholar, respectively. The next step was a selection based on the relevancy, accessibility, and the languages of the articles, where the articles reviewed were only in English. Furthermore, related references in the articles were also reviewed in order to broaden the search. This strategy resulted in 24 eligible articles from the past 30 years.

RESULTS

The data gathered from the articles consisted of the author (year of publication), study design, age and gender of the study population (for the age we used: mean ± SD or median [IQR]), indication for the cardiac/open chest surgery, and the outcome (sternal healing).

Of the 24 articles cited to be reviewed, most of the studies (n = 19) were observational, and the rest were literature reviews (n = 3) and systematic reviews/meta-analyses (n = 2). Almost all papers showed that CABG was the most common cardiac surgery performed, followed by valve reconstruction, aortic/other vessel surgeries, emergency surgeries, heart transplantation, and others (unmentioned); one study by Zahiri *et al.* that investigated the sternum reconstruction using the autologous flap.[28]

DISCUSSION

Comorbidities Associated with Diabetes Mellitus

In general, the complications exerted by a person with chronic diabetes mellitus are classified into microvascular and macrovascular involvements. The diabetic microvascular pathophysiology is associated with many chronic inflammatory processes triggered by some cytokines and growth factors.[35-43] Increased levels of glucose will further increase the production of advanced glycation end product (AGE); this substance has several deleterious effects, one of which is to directly cross-link the collagenous portion beneath the vascular wall. This non-enzymatic reaction, if it occurs for a long period, will result in microangiopathy–characterized by the thickening and infiltration of immunological cells of the small blood vessels that can be found in the retina, skin, and glomerulus. AGE will also bind to its receptor (RAGE), expressed mainly on osteoclasts and osteocytes; the activation of RAGE will lead to osteoclastogenesis. Thickened and occluded vascular lumen will lead to poor tissue and connective tissue perfusion, including the tissue of the skin, bone, and peripheral nerves.[44]

A hyperglycemic state will also promote the formation of intracellular fructose and sorbitol via the sorbitol (polyol) pathway, particularly in the non-insulin-dependent tissues (endothelial cells, neurons and peripheral nerve cells, pancreatic β-cells, and kidney). Excess glucose will be first converted to sorbitol by an enzyme called aldose reductase. Next, the sorbitol is oxidized by sorbitol dehydrogenase into fructose as the final product. Accumulation of these substances inside the cells will result in an osmotic pressure gradient that eventually damages the cell membrane; moreover, this enzymatic reaction utilizes nicotinamide adenine dinucleotide phosphate (NADPH) that is also needed to make GSH (glutathione), a potent antioxidant; hence, increased polyol reaction as seen in diabetes will promote the excess formation of reactive oxygen species (ROS) while decreasing the rate of its degeneration, making the cells previously mentioned injured and damaged.[45]

Immune disruption is also seen in diabetic patients. Several experimental and *in vitro* studies have shown that the excess blood glucose level will impair cytokine formation, defect in leukocytes recruitment and activation at the injured site, and wound healing along with tissue regeneration. Diabetic patients also reflect poor immunological performance in terms of eradicating infection, which mainly involves the activation and effective signaling of macrophages and natural killer cells. This also could explain the common incidence of both superficial and deep wound infections and poorer prognosis of diabetics in facing severe infectious agents compared with normoglycemic individuals.[11,14,46]

Sternal Healing

The bone healing process consists of four stages: inflammation, soft callus formation, complex callus formation, and bone remodeling.[47] Bony compartments can achieve optimal healing in several ways after getting injured or in the case of fracture, namely intramembranous and endochondral ossification. Intramembranous ossification is one of the healing processes that mainly requires the direct differentiation of mesenchymal precursor cells (MPC) to osteoblasts without going through the cartilaginous phase – which is not the case of endochondral ossification, which undergoes cartilaginous phase (the proliferation of MPCs to chondrocyte first). Intramembranous ossification occurs notably in flat bones (e.g., sternum and cranial bone). Meanwhile, endochondral ossification usually takes place at the long (diaphyseal) bones (femur and tibia).[48,49]

Several factors that influence the normal bone healing process are proper oxygenation, adequate supply of various nutrients consisting of glucose & other mineral components, and activity of the nearby precursor cells that secrete growth factors needed to assemble the new tissue. These events are orchestrated well only if good perfusion exists, which is not the case with chronic diabetes.[49,50]

Besides biological factors, physical/mechanical factors also influence the outcome of a bone healing process. The sternum is anatomically located at the

anterior, midline chest and is also a crucial part of the rib cage. Furthermore, it has an important barrier function towards the underlying vital organs that comprise the heart, great vessels, and pulmonary tissues. The rib cage itself is slightly mobile since it moves on several occasions: breathing, coughing, and when one individual lift a heavy object. This makes the sternum tends to be strained and stretched most of the time, leading to lateral distraction.[49,51]

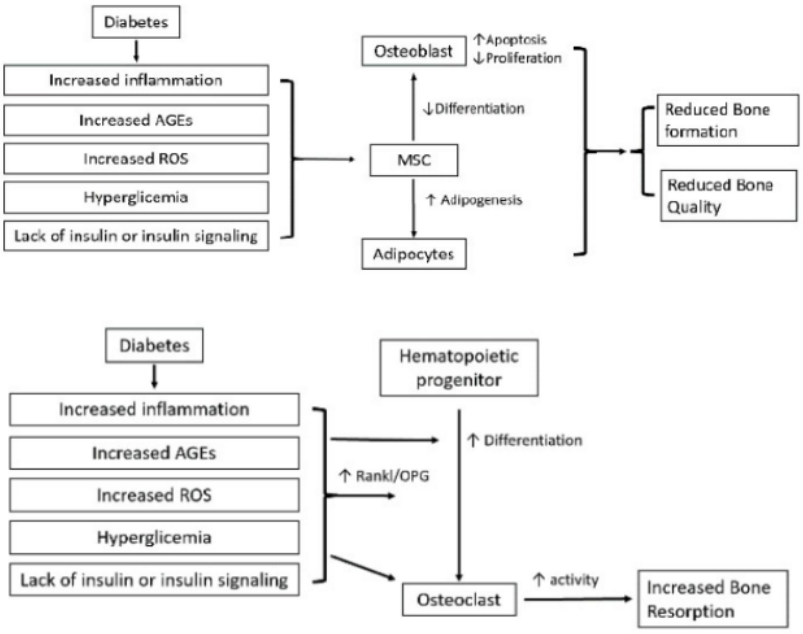

Figure 1. Diabetes affects cellular components of the sternal bone healing.

Diabetes Mellitus and Sternal Wound Impairment

Normally, circulating insulin exerts its anabolic effect on the bone by binding with INSR/IRS-1 expressed on osteoblasts. After binding, the subsequent event will be the activation of Akt and PI3K with appropriate suppression of the FOXO1 gene. Decreased level of insulin, either because of the lack of production or ineffective utilization, will lead to the impairment of normal bone growth that is characterized by abnormal mineralization and matrix deposition along with the abnormality of bone architecture. These abnormalities are prominently seen among T1DM patients since this population totally lacks insulin production.[42,52]

After an injury, the bone will develop an intramedullary hematoma, by which this event is purposed to effectively recruit inflammatory cells and adjacent fibroblasts. Bone mineralization, along with inorganic matrix deposition, occurs with the help of these cells and requires high content of collagen, notably type I. AGE, a protein glycosylated with the aldose sugar, directly cross-linked the exposed collagen and halted its utilization by fibroblasts and macrophages, decreasing the collagen's availability within the injured bony tissue.[52,53]

The abnormally high level of proinflammatory cytokines (IL-6, TNFα), AGE, along with the accumulation of intracellular ROS, will disrupt the differentiation of mesenchymal stem cells (MSC) and survivability of osteoblasts. High levels of cytokines and alterations in growth hormone secretion also will shift the differentiation from osteoblastic to the osteoclastic direction, worsening the performance of the bone healing process even further. Osteoclastogenesis occurs due to the activation of RAGE, and as a consequence, the production of Receptor Activator of Nuclear Factor κ-B (RANK) by nearby osteocytes and osteoblasts is increased. RANK binds to its ligand (RANKL), which is located along the osteoclast cellular membrane. RAGE also down-regulates the expression of osteoprotegerin (OPG) to enhance osteoclastogenesis and bone resorption.[52,54,55]

Previous Studies Related to Sternal Healing Outcome

Out of 24 articles reviewed, as shown in Table 1, most of the works of literature found that diabetes, regardless of the type, was significantly associated with the incidence of sternal wound complications that comprise sternal dehiscence and infection (superficial and deep), and malunion.[11,13-15,18-23,25,28-31,34] This corresponds with the previously postulated theory regarding the multiorgan and immunological dysfunction associated with a hyperglycemic state. Some studies, however, stated that the type of diabetes was more significant in T1DM rather than T2DM. This suggests that lacking insulin condition was more severe among T1 diabetes patients compared to T2 diabetics.[16,21,42,52] Other contradictory results were reported, where significance between the incidence of sternal wound complication was not associated with diabetes mellitus.[10,17,24,26,27,32,33] Some studies mentioned that besides diabetes, the outcome of sternal healing among patients receiving CABG procedure also depended on the grafting technique, particularly if internal mammary arteries, which is the first choice of conduit, were used as the vessel source since the major vascularization of the sternum was derived from these arteries.[20,24,34,55]

Evaluation for Sternal Healing

Several parameters were set to evaluate the outcome of sternal healing, comprised of sternal wound infection (superficial and/or deep), sternal dehiscence, and sternal instability. According to National Nosocomial Infections Surveillance (NNIS), superficial infection is defined as an infection that involves the skin (epidermis and dermis) and the subcutaneous layer that is clinically assessed by at least 1 (one) finding as follows: 1) purulent discharge, 2) positive culture result from the discharge, 3) erythema, pain/tenderness and warm

sensation that surrounds the incision site, and 4) surgeon's decision.[23,39,31] Deep sternal infection based, on the Centers for Disease Control and Prevention (CDC), is defined where the subcutaneous tissue and the space underneath it are involved, with at least one of the following criteria: 1) positive culture/organism isolation from mediastinal tissue, 2) clinical signs of mediastinitis, and 3) systemic manifestation such as fever (body temperature of ≥ 38°C), sternal/chest pain, and/or sternal instability. Almost all studies used these criteria to diagnose sternal wound infection after open cardiac surgery.[11-14,16-22,25-34] CT scan was used by Shin *et al.* to investigate the sternal healing that was proved by the union of the sternal body and manubrium.[15] Culture and pathogen identification from the mediastinal and the incisional discharge was conducted by Heilmann *et al.*, Zacharias *et al.*, and Fakih *et al.*, with most of the pathogens isolated, were methicillin-susceptible *S.aureus* (MSSA), coagulase-negative staphylococci, gram-negative aerobes, *Corynebacterium sp.*, and *Candida sp.*[16,23,31]

CONCLUSION

Open heart surgery is a major invasive procedure that has several complications that are broadly categorized into local and systemic. The most common local involvement is impaired sternal healing. It can be caused by many factors. One of them is diabetes mellitus with chronic hyperglycemia. The literature review results showed that chronic hyperglycemia could lead to several organ damages and immunological dysregulation, resulting in defective bone repair, perfusion, and ineffective remodeling.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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ETHICS APPROVAL

Not applicable.

AUTHOR CONTRIBUTION

Taufik Nur Yahya, Yan Efrata Sembiring, and Soebagijo Adi Soelistijo conceptualized and designed the study. All authors analyzed and interpreted the study results and revised the manuscript.

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Table 1. Clinical characteristics of populations included in this study.

No	Author (year)	Design	Age (year)	Gender (year)	Indication(s) of Surgery	DM Type	Outcome
1	Lemaignen *et al.*[11] (2015)	Observational	65.6 [55.4–74.9]	Male & Female	Cardiac surgeries: surgical emergency, isolated valve surgery, isolated CABG, valve + CABG & others.	Type I (insulin-dependent) and Type II	Diabetes mellitus (both non-insulin and insulin-dependent) were significantly correlated with sternal wound infection and wound healing impairment ($p<0.001$)
2	Sofer *et al.*[12] (1999)	Observational	≥65	Female	CABG	NS	Advanced age and the presence of diabetes mellitus were not significant risk factors for sternal wound infection (SWI).
3	Oswald *et al.*[13] (2012)	Meta-analysis	>65	Female	CABG	NS	CABG in patients with diabetes mellitus was strongly associated with sternal wound healing impairment.
4	Balachandran *et al.*[14] (2016)	Systematic Review	≥18	Male & Female	Cardiac surgeries: valve surgery, CABG, valve + CABG	Type I (insulin-dependent) and Type II	Impaired sternal healing and wound infection were significantly correlated with diabetes mellitus, both non-insulin and insulin-dependent
5	Shin *et al.*[15] (2015)	Observational	64.4	Male & Female	CABG	NS	Diabetes mellitus was strongly associated ($p<0.05$) with poor sternal healing.
6	Heilmann *et al.*[16] (2013)	Observational	67.0 ± 12.7	Male & Female	Cardiac surgeries: surgical emergency, isolated valve surgery, isolated CABG, valve + CABG & aortic operations	Type I (insulin-dependent) and Type II	Type I diabetes mellitus but not type II was associated with both postoperative superficial SWI and deep SWI. The other contributing factors were obesity and COPD.
7	Gansera *et al.*[17] (2016)	Observational	60.1 ± 5.3	Male	CABG	Type I (insulin-dependent) and Type II	Even though both types (I&II) DM patients had a higher risk of developing deep SWI after sternotomy, it did not reach clinical significance. There was also no significant correlation between BIMA (bilateral IMA grafting) and SIMA grafting method with long-term outcomes among diabetics who underwent CABG.

No	Author (year)	Design	Age (year)	Gender (year)	Indication(s) of Surgery	DM Type	Outcome
8	Zalewska-Adamiec *et al.*[18] (2014)	Observational	69.7 ± 6.75	Male	CABG	Type I (insulin-dependent) and Type II	Wound healing defect and sternal dehiscence were significantly higher among diabetics (both types) compared with non–diabetics.
9	Nakano *et al.*[19] (2008)	Observational	69.3 ± 8.1	Female	Cardiac surgeries: surgical emergency, isolated valve surgery, isolated CABG, valve + CABG & aortic operations	Type I (insulin-dependent) and Type II	Sternal wound infection and healing impairment were significantly higher among diabetics than non–diabetics.
10	Peterson *et al.*[20] (2003)	Observational	60.1 ± 9.3	Male	CABG	Type I (insulin-dependent and Type II	Sternal healing impairment and healing complications were significantly lowered among diabetics that received skeletonized IMA grafts rather than non-skeletonized.
11	Zacharias *et al.*[21] (1996)	Observational	63	Male & Female	Cardiac surgeries: CABG only, the valve only, others	Type I (insulin-dependent) & Type II	Diabetes mellitus, mainly insulin-dependent (type I), was strongly associated with the incidence of SWI after cardiac surgery.
12	Pevni *et al.*[22] (2008)	Observational	>70	Male & Female	CABG	Type I (insulin-dependent) & Type II	Diabetic patients had a strong association with the incidence of SWI.
13	Zuckermann *et al.*[23] (2011)	Review	NS	Male	Heart transplantation	NS	Diabetic patients undergoing heart transplantation have a higher incidence of deep SWI and also a higher risk (Odds ratio/OR; 2.1 – 5.5)
14	Lazar *et al.*[24] (2018)	Review	NS	Male & Female	CABG	NS	There was no significant difference between diabetic and non-diabetic in deep sternal wound healing. This was suggested to be correlated with the method used – skeletonization, by which it preserved collateral circulation to the sternum.
15	Fu *et al.*[25] (2015)	Observational	65.6 ± 15.7	Male & Female	Cardiac surgeries: elective & emergency surgeries, IMA grafting	NS	Diabetic patients that require medication, BMI > 30, respiratory disorders, and emergency surgery were significant predictors of sternal wound dehiscence.

No	Author (year)	Design	Age (year)	Gender (year)	Indication(s) of Surgery	DM Type	Outcome
16	Gurevitch *et al.*[26] (1999)	Observational	65	Female	CABG	NS	Sternal wound infection and healing impairment were not significantly correlated with diabetes mellitus and advanced age (>65 years old). Healing impairment was only encountered in 30% of patients.
17	Shaheen *et al.*[27] (2020)	Observational	60 ± 1.25	Male & Female	CABG	NS	Superficial and deep sternal wound infections along with impaired healing were seen more commonly among diabetic patients, although P-value didn't reach a significant value (P>0.05)
18	Zahiri *et al.*[28] (2012)	Observational	61.8	Male & Female	Sternal Wound Reconstruction	NS	Sternal wound complication after flap reconstruction was 2.6 times more frequently to be encountered among diabetics.
19	Lenz *et al.*[29] (2016)	Observational	NS	NS	CABG	Type I (insulin-dependent) & Type II	Sternal wound infections (superficial and deep) were significantly higher in diabetic patients, mainly insulin-dependent diabetes mellitus
20	Savage *et al.*[30] (2007)	Observational	64.6 ± 10.2	Male & Female	CABG	Type I (insulin-dependent) & Type II	The incidence of deep sternal wound complications was significantly higher in patients with diabetes mellitus, especially in insulin-dependent diabetics.
21	Fakih *et al.*[31] (2007)	Observational	67.2 ± 11	Male	CABG	NS	Deep and superficial SWI were encountered more frequently in candidates with diabetes mellitus (p<0.005).
22	Sakamoto *et al.*[32] (2003)	Observational	62.0 ± 11.9	Male	Cardiac surgeries: surgical emergency, isolated valve surgery, isolated CABG, valve + CABG & aortic operations	NS	This study showed no significant correlation between DM and deep sternal wound infection
23	Kieser *et al.*[33] (2014)	Observational	65 ± 10.4	Male & Female	CABG	Type I insulin-dependent) & Type II	There was no significant impact of diabetes mellitus on the incidence of deep SWI both in male and female diabetics.

No	Author (year)	Design	Age (year)	Gender (year)	Indication(s) of Surgery	DM Type	Outcome
24	Dai *et al.*[34] (2013)	Review	>65	NS	CABG (BIMA & SIMA)	NS	Patients with diabetes mellitus had more adverse and extended sternal wound complications after undergoing CABG surgery,

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