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MINIREVIEWS

Effects of medically generated electromagnetic interference from medical devices on cardiac implantable electronic devices: A review

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Abstract

As cardiac implantable electronic devices (CIED) become more prevalent, it is important to acknowledge potential electromagnetic interference (EMI) from other sources, such as internal and external electronic devices and procedures and its effect on these devices. EMI from other sources can potentially inhibit pacing and trigger shocks in permanent pacemakers (PPM) and implantable cardioverter defibrillators (ICD), respectively. This review analyzes potential EMI amongst CIED and left ventricular assist device, deep brain stimulators, spinal cord stimulators, transcutaneous electrical nerve stimulators, and throughout an array of procedures, such as endoscopy, bronchoscopy, and procedures involving electrocautery. Although there is evidence to support EMI from internal and external devices and during procedures, there is a lack of large multicenter studies, and, as a result, current management guidelines are based primarily on expert opinion and anecdotal experience. We aim to provide a general overview of PPM/ICD function, review documented EMI effect on these devices, and acknowledge current management of CIED interference.

Key Words: Electromagnetic interference; Pacemaker; Implantable cardioverter defibrillator; Permanent pacemakers; Cardiac implantable electronic devices; Left ventricular assist device; Endoscopy; Bronchoscopy; Electrocautery; Capsule endoscopy; Transcutaneous electrical nerve stimulators unit; Spinal cord stimulator

Core Tip: There are several infrequent yet significant sources of electromagnetic interference (EMI) on cardiac implantable electronic devices (CIED). These include both implantable devices and procedures. Patients with cardiac devices often may need another implanted medical device or specific medical procedures. The potential resulting EMI can be minimized in order to make these treatments safer and still provide patients with therapeutic relief. A large, prospective study is critical to provide more robust and consistent literature regarding EMI effects on CIED. This will provide a clearer assessment of risk of EMI associated with variety of sources in addition to the development of evidence based clinical guidelines regarding management of patients with CIED.

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INTRODUCTION

Cardiac implantable electronic devices (CIED) include two main broad categories of devices, implantable cardioverter defibrillators (ICD), and permanent pacemakers (PPM)[1]. Over the last decade, the indications for the use of these devices have increased. Since 2019, over three hundred thousand devices have been implanted every year alone in the United States[2]. Hence, it is important for clinicians to recognize challenges involved in the management of these devices. One of the biggest challenges with these is electromagnetic interference (EMI), which occurs as a result of exposure of a CIED to an electromagnetic signal from other devices such as a smartphone, metal detector, taser, headphones and less frequently from internal and external medical devices, and surgical procedures. EMI can lead to inappropriate CIED function and have catastrophic consequences[3]. EMI can be interpreted by PPM as an intrinsic cardiac signal and result in inhibition of pacing, leading to bradycardia, and potentially cardiac arrest[3]. Similarly, EMI in patients with ICD can lead to inappropriate shocks due to perceived ventricular tachyarrhythmia[3]. The aim of this 2-part review article is to discuss the infrequent sources of EMI: (1) From implantable devices; and (2) Surgical procedures, its interactions with CIEDs, and management options to prevent these undesirable consequences.

CIED INDICATIONS AND OVERVIEW

As PPM and ICD become more prevalent, it is important to briefly review indications and general functionality of these devices. According to the ACC/AHA/HRS guidelines, PPM are most commonly indicated for sinus node dysfunction, symptomatic bradycardia, and atrioventricular block[4]. The indications for ICD placement are divided into primary and secondary prevention[5,6]. Primary prevention focuses on those patients who are at high risk for sudden cardiac death as a result of ventricular tachyarrhythmias. This typically includes patients with cardiomyopathies who are classified in New York Heart Association functional classes II and III with a left ventricular ejection fraction of 35% or less. Secondary prevention is indicated for those patients with documented prior episodes of hemodynamically unstable ventricular arrhythmias of unknown etiology and in patients with sustained ventricular arrhythmias and heart disease[5,6].

PPM and ICD are composed of a few components: generator, lead(s), an electrode at the tip of each lead, and, if an ICD, a shocking coil(s). The generator is located in the subcutaneous tissue of the upper chest wall or under the pectoralis major and is responsible for the generating a current that is transmitted by the leads. Leads may be inserted into one or more chambers of the heart depending on the type of CIED that is indicated. Each lead tip is in direct contact with the cardiac myocytes, and these leads are either unipolar or bipolar. A unipolar lead is a single conductor lead that transmits electricity in a unidirectional fashion, meaning the generator serves as the anode and the lead tip as the cathode with electrons flowing from anode to cathode[7]. A bipolar lead has two isolated conductors on the tip with one serving as the anode and the other as the cathode.

CIED RESPONSE TO INTERNAL AND EXTERNAL DEVICES

There has been longstanding concern and scrutiny throughout the electrophysiology, chronic pain management, and physical rehabilitation communities in regard to potential electrical interference

amongst internal and external medical devices, in particular left ventricular assist devices (LVADs), CIED, deep brain stimulators, transcutaneous electrical nerve stimulation (TENS) units, and spinal cord stimulators. We have summarized some of these concerns in Table 1. In regard to LVADs, Erquo *et al*[8] presented the case of 60-year-old female patient with doxorubicin-induced dilated cardiomyopathy status post cardiac resynchronization therapy defibrillator who underwent LVAD pump exchange. The intraoperative exchange was uncomplicated; however, postoperatively it was noted that the patient was in complete heart block with her pacemaker no longer consistently pacing. The loss of consistent pacing was found to be secondary to increased RV lead sense amplification from the LVAD's pump rotation speed. To mitigate the pacemaker's oversensing, the low frequency attenuation filter was disabled, which allowed the device to function without further inhibition. Additionally, Pfeffer *et al*[9] outlined additional LVAD-ICD interference; however, this case differs from Erquo *et al*[8] as it described the interaction between subcutaneous ICD and LVAD. This case involved a 42-year-old male with nonischemic cardiomyopathy who received 31 ICD shocks one hour after LVAD placement. This adverse interaction was due to superimposed electric noise from the LVAD in the setting of diminished R waves. This mixing of electrical noise was perceived as a shockable rhythm by the S-ICD. This patient's S-ICD was removed and a transvenous ICD was placed, which resulted in regular device function and no further ICD shocks on 6-month follow-up.

In addition, deep brain stimulators (DBS) and spinal cord stimulators (SCS) are becoming more prevalent as well. However, their adverse interactions with PPM and ICD are not well-documented. There are case reports that demonstrate a safe coexistence between CIED and DBS or SCS. Obwegeser *et al*[10] demonstrates the safety of DBS in a patient being treated for essential tremor in the setting of a previously implanted ICD for sustained monomorphic ventricular tachycardia. This patient's DBS pulse generator was in close proximity of the ICD (10.5 cm away); however, after thorough testing, there was no inappropriate sensing by the ICD. The safety of DBS and ICD is further supported by Elliot *et al*[11], who analyzed 20 case reports with sub-clavicular DBS and PPM/ICD (some locations not stated) and found no effect of the DBS on a cardiac device; however, in one case a single ICD shock resulted in the deactivation of bilateral DBS devices. SCS also appear to safely coexist with PPM/ICD as demonstrated by Schimpf *et al*[12]. They noted no oversensing of the impulses from the SCS by ICD or SCS device failure after an ICD-shock. Unipolar or bipolar stimulation from the SCS in different voltages or impulse rates resulted in no oversensing or adverse interaction with ICD function. There was potentially some concern for SCS used at the cervical level to induce probable interference with ICD/PPM given their proximity; however, a report by Thomas *et al*[13] found no potential interaction between cervical SCS with ICD in five swine models. No reports of cervical SCS adverse interactions with ICD are available in human patients.

In contrast to DBS and SCS, there are more reported adverse interactions between CIED and TENS units. Both Singh *et al*[14] and Shenoy *et al*[15] reported EMI from a TENS unit that resulted in an ICD shock. Singh *et al*[14] details a S-ICD shock after a patient underwent TENS therapy in the neck, axilla, and back. This adverse interaction was likely due to the relatively superficial location of the S-ICD and its increased susceptibility to EMI, which ultimately led to an ICD shock after the device detected low-amplitude and high frequency signals[14]. Shenoy *et al*[15] further documents ICD and TENS interaction even in a patient with a transvenous ICD, who underwent TENS therapy in an unreported anatomic location. A single shock occurred during TENS therapy. Device interrogation revealed low-amplitude sinusoidal electrical activity during the patient's muscle therapy, leading to an ICD shock [15]. These two reports support the increased risk of EMI-induced shock delivery from an ICD whether subcutaneously or transvenously placed. Similarly, past reports have analyzed a potential interaction between TENS units and pacemakers, and a general consensus was contraindication of TENS units in individuals during synchronous pacing but safety while use in those with asynchronous pacing.

In summary, the above studies suggest a low risk of EMI from DBS or SCS on CIED function. However, there is a greater risk of EMI arising from LVADs on pacemakers and defibrillators, and from TENS unit on defibrillators and certain older generation pacemakers as summarized in Table 2.

In order to minimize the interaction between stimulators (DBS, TENS unit, SCS) and CIED that is implanted, the parameter for each device should be assessed under "worst case scenario" settings. The stimulator is programmed to its maximally tolerated output while the cardiac device is programmed to its maximal sensitivity to assess for the effect of EMI. Once this effect is determined, the output from the stimulator should be decreased to the minimal value that will achieve therapeutic benefit and the sensitivity of the CIED is also decreased to prevent detection of stimulator output yet recognize underlying cardiac activity. In regard to LVAD, following the optimization of the LVAD function, the sensitivity of the CIED is adjusted to minimize detection of EMI, sense R waves and allow for differentiation of R waves from T waves. Furthermore, in LVAD patients, RV pacing is preferential over biventricular pacing, as RV pacing has been associated with improved functional status, better quality of life, fewer arrhythmias, and potentially less EMI[16].

Table 1 Internal and external device interaction with permanent pacemakers / defibrillators

	Erquo *et al*[8], 2018	Pfeffer *et al*[9], 2016	Obwegeser *et al* [10], 2001	Shenoy *et al*[15], 2017	Singh *et al*[14], 2018	Schimpf *et al* [12], 2003
Internal/ External Device	St. Jude; CRT-D	Boston Scientific; S-ICD	Medtronic dual chamber ICD	Durata dual chamber ICD	Boston Scientific; S-ICD;	Medtronic dual chamber ICD
EMI Source	LVAD (pump exchange)	LVAD placement	Thalamic DBS	TENS unit (unreported location)	TENS unit on neck, back, axilla	T11 SCS
Adverse Interaction	Ventricular oversensing leading to inhibition of pacing	Oversensing leading to 31 ICD shocks	None	EMI leading to ICD shock	EMI leading to ICD shock	None
Therapeutic intervention	Turning off low-frequency attenuation filter	Transvenous ICD placement	N/A	Avoiding TENS units	Avoiding TENS units	N/A

PPM: Permanent pacemaker; LVAD: Left ventricular assist device; ICD: Implantable cardioverter-defibrillator; CRT-D: Cardiac resynchronization therapy defibrillator; S-ICD: Subcutaneous implantable cardioverter-defibrillator; DBS: Deep brain stimulator; N/A: Not applicable; TENS: Transcutaneous electrical nerve stimulation; SCS: Spinal cord stimulator.

Table 2 Device interaction on pacemaker and defibrillators

Type of device	Pacemaker	Defibrillators
LVADs	+	+
SCS	-	-
DBS	-	-
TENS	+	+

(-): No EMI noted; (+): EMI noted. LVAD: Left ventricular assist device; DBS: Deep brain stimulator; TENS: Transcutaneous electrical nerve stimulation; SCS: Spinal cord stimulator.

SURGICAL PROCEDURES ASSOCIATED EMI WITH CIED

Over the years, numerous studies have been conducted aiming to better understand the role of electromagnetic interference from surgical procedures with CIED. In this section, we will review the available literature relating to the EMI caused by various surgical procedures including endoscopy, bronchoscopy, electrosurgery and its interaction with CIEDs (Table 3).

Endoscopies have revolutionized the field of gastroenterology by allowing clinicians to effectively diagnose and manage diseases of the gastrointestinal tract. Radiofrequency energy modality is commonly utilized by gastroenterologists during endoscopies to achieve hemostasis. This therapeutic modality has been a cause of concern for clinicians as a potential source of EMI that can interfere with CIED. To elucidate this potential interaction, Samuels *at el*[17]. performed a Manufacturer and User Facility Device Experience (MAUDE) query between 2009-2019, and noted 45 reports of EMI causing CIED malfunction during endoscopy, which included 26 inappropriate shocks (65%), and less frequently, bradycardia, and asystole[17]. In contrast, there have been smaller individual retrospective and prospective studies performed to evaluate EMI during endoscopy in patients with CIED which found no adverse interaction. In a study by Guertin *et al*[18], 41 patients with ICDs underwent endoscopies with ICDs programmed to detection-only with abortive (or therapeutic) tachyarrhythmia therapies off. Post-procedural device interrogation noted no EMI or arrhythmic events triggered during the procedure[18]. Similarly, in a large cohort study of 92 patients by Cheng at al. there were no observed adverse events on patients with defibrillators. Among the patients with a pacemaker, they observed three cases of EMI that was interpreted by the pacemaker as rapid atrial activity, which resulted in mode switching from dual chamber pacing to ventricular pacing and two cases of detection of EMI as rapid ventricular activity resulting in inhibition[19]. Even though these cohort studies have shown the safety of the use of CIED during endoscopy, Samuels *et al*[17] study clearly demonstrates a small risk of CIED dysfunction and inappropriate shock that was not observed in the aforementioned studies. These three studies demonstrate the potential effects of EMI during endoscopy with electrocautery on both pacemaker and ICD function. Therefore, until large multicenter studies are performed, clinicians should be aware of the potential risk of an CIED adverse event during these procedures. To mitigate the risk, reprogramming the device or magnet therapy is recommended, which will be

Table 3 Suggested cardiac implantable electronic devices peri-procedural management

Procedure	CIED (PPM)	CIED (ICD)
Endoscopy	Asynchronous	*R* or Magnet
APC	Asynchronous	*R* or Magnet
ENB	*b*	*b*
Electrocautery	Asynchronous	*R* or Magnet

APC: Argon plasma coagulation; ENB: Electromagnetic navigational bronchoscopy; *b*: Contraindicated; *R*: Reprogramming; CIED: Cardiac implantable electronic devices; PPM: Peri-procedural management; ICD: Implantable cardioverter defibrillators.

discussed later in more detail.

The introduction of capsule endoscopy has transformed the field of gastroenterology as well; however, similar concerns of EMI during this procedure have been raised. Reassuringly, in a cohort study by Harris *et al*[20] of 118 patients undergoing capsule endoscopy, no interference with CIED was reported. To further support the safety of capsule endoscopy, Bandorski *et al*[21], performed an in-vitro investigation, in which they placed capsules used during the procedure at various distances to the lead and ICD device, and monitored device activity continuously. Interestingly, even at the closest proximity to the ICD (on top of the device), no interference was observed. However, similar to traditional endoscopy, no large studies have been performed evaluating EMI with CIED, therefore reprogramming the device may be appropriate during the procedure.

Over the last two decades, the field of interventional pulmonology has rapidly expanded. Procedures and modalities such as laser therapy, argon plasma coagulation, electrocautery, and electromagnetic navigational bronchoscopy (ENB) are being performed at higher rates than ever before. These procedures use heat and electrical energy and can produce an electromagnetic field which can generate EMI and affect devices in the vicinity, especially CIED. There are concerns of APC and electrocautery causing EMI given its configuration of current delivery. Electrocautery during bronchoscopy has two main modes of current delivery: monopolar and bipolar. In monopolar configuration, current "entry" is delivered by the cauterizing instrument and leaves through the "ground" electrode, that is typically placed somewhere on the body (often the legs). In the monopolar configuration, the current has to pass through a large body surface area and can cause significant EMI, and ICDs can spuriously interpret the EMI as a tachyarrhythmia and result in an unnecessary shock. EMI in PPM can lead to inhibition of pacing, mode-switching, or reprogramming. EMI can be avoided if bipolar current configuration is used as the "entry" and "exit" electrodes are located at the tip of the cauterizing instrument, allowing for a very narrow EMI field. Similar to the monopolar configuration of the electrocautery, APC only has monopolar circuitry, causing a high risk of EMI. Lastly, per CHEST guidelines, ENB is contraindicated in patients with CIEDs given the electromagnetic field that it creates around the subjects[22]. To better understand EMI from ENB, an in-vitro test was subsequently performed by Magnani *et al*[23]. They noted insignificant EMI, with no interaction with CIEDs. However, this test was performed using a human torso simulator, with no replicative studies performed in humans due to the theoretical risk of CIED dysfunction given the large electromagnetic field that is created during these procedures. Overall, clinicians must be aware of the potential EMI leading to CIED malfunction during bronchoscopies.

Similar to bronchoscopy, electrosurgery is commonly used during surgical procedures to cut or coagulate tissue. The current configuration of electrosurgery is either monopolar or bipolar as stated above. Therefore, individuals undergoing any surgical intervention including general surgery, cardiac surgery, abdominal surgery, etc. are at risk of EMI with CIEDs, if monopolar current configuration is used by the operator. In addition to the monopolar current configuration, another factor that increases the likelihood of EMI with CIEDs is the distance between the surgical field where electrosurgery is being performed and the location of the CIED. In a study of 171 patients with ICDs, EMI was noted with monopolar configurations in 9 of 22 procedures above umbilicus, but in none of fifty-three patients below umbilicus[3]. For procedures in close proximity to the CIED, temporary reprogramming is recommended and will be discussed in the subsequent section. Recent HRS/ASA guidelines suggest that for procedures below the umbilicus, given the low concern for EMI, reprogramming is not recommended[24]. Further detailed management of CIED interference will be discussed in the following section.

PERI-PROCEDURAL MANAGEMENT OF CIED INTERFERENCE

Due to the potential detrimental effects that EMI can cause with CIEDs, this section will discuss the interventions that can be applied to minimize and/or prevent EMI in CIEDs. The recommendations are generally based on expert opinion as there are no large multicenter studies performed to address EMI

that occurs in patients with CIED[25].

Prior to any procedure, patients with CIED should undergo CIED interrogation within 6 to 12 mo to identify the type of cardiac device implanted and if the patient is device dependent[17,25], which will ultimately dictate intraoperative and postoperative management.

The ACC/AHA guidelines recommend placing the device into an asynchronous mode for the entire duration of the procedure in device dependent patients who are undergoing EMI-generating procedures, whereas ASGE suggests it should be reserved only for prolonged (no specific length of time provided) endoscopy procedures in these patients[17]. Asynchronous modes include dual chamber asynchronous pacing, asynchronous ventricular pacing, or asynchronous atrial pacing. These modes mitigate the potential adverse EMI that can result in intermittent of loss of pacemaker function *via* delivery of a constant, fixed stimulus without sensing capability. The pulse generator will then send a constant pacing stimulus regardless of external electrical influence. In addition, reprogramming or inactivating the tachyarrhythmia detection/management of ICDs is recommended. If this is not feasible, placing a cardiac magnet over the pulse generator is an alternative method[26]. All CIED are fitted with a reed switch comprised of two magnetic metal strips that are separated. When these strips are activated *via* the application of a magnetic field, they come into contact, preventing sensing by a pacemaker resulting in asynchronous pacing and inhibition of ventricular tachyarrhythmia detection and prevention of shock delivery by an ICD[25,26]. Once the magnet is removed, the device will return to its pre-magnetic application modes/settings. Post-procedure management involves CIED interrogation and restoration of the devices to their original settings and pre-procedural therapeutic thresholds and sensing if they were reprogrammed before the procedure[25].

In addition, the expert consensus statement by HRS/ASA further recommends any procedures associated with EMI that are performed geographically above the umbilicus, such as bronchoscopy, should also undergo the post-procedure management as described above[25].

LIMITATIONS

While there is evidence to support concern for EMI on CIEDs, the literature primarily is comprised of case reports or small case series reviews. Therefore, the data regarding the risk of EMI from medical devices or procedures is often sparse and inconsistent. For instance, the MAUDE query performed by Samuels *et al*[17] demonstrates a small risk of EMI on CIEDs during endoscopic procedures. However, given the limited quality of data available in the database it is difficult to identify the exact etiology of and clinical scenario surrounding each reported CIED malfunction[27]. There are also conflicting studies reporting no adverse events during endoscopic procedures, thus it is challenging to conclude the true risk of significant EMI during endoscopy. Similar conflicting reports exist for a number of interventions suspected to interfere with CIEDs. Additionally, as a result of limited data, consensus recommendations from the HRS/ASA regarding management of CIED interference are heavily reliant on personal experience of prior patient management.

CONCLUSION

There are several infrequent yet significant sources of EMI on CIED. These include both implantable devices and procedures. Patients with cardiac devices often may need another implanted medical device or specific medical procedures. The potential resulting EMI can be minimized in order to make these treatments safer and still provide patients with therapeutic relief. A large, prospective study is critical to provide more robust and consistent literature regarding EMI effects on CIED. This will provide a clearer assessment of risk of EMI associated with variety of sources in addition to the development of evidence based clinical guidelines regarding management of patients with CIED.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

SVEAT score outperforms HEART score in patients admitted to a chest pain observation unit

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Abstract

BACKGROUND

Timely and accurate identification of subgroup at risk for major adverse cardiovascular events among patients presenting with acute chest pain remains a challenge. Currently available risk stratification scores are suboptimal. Recently, a new scoring system called the Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin (SVEAT) score has been shown to outperform the History, Electrocardiography, Age, Risk factors and Troponin (HEART) score, one of the most used risk scores in the United States.

AIM

To assess the potential usefulness of the SVEAT score as a risk stratification tool by comparing its performance to HEART score in chest pain patients with low suspicion for acute coronary syndrome and admitted for overnight observation.

METHODS

We retrospectively reviewed medical records of 330 consecutive patients admitted to our clinical decision unit for acute chest pain between January 1st to April 17th, 2019. To avoid potential biases, investigators assigned to calculate the SVEAT, and HEART scores were blinded to the results of 30-d combined endpoint of death, acute myocardial infarction or confirmed coronary artery disease requiring revascularization or medical therapy [30-d major adverse cardiovascular event (MACE)]. An area under receiving-operator characteristic curve (AUC) for each score was then calculated. C-statistic and logistic model were used to compare

predictive performance of the two scores.

RESULTS

A 30-d MACE was observed in 11 patients (3.33% of the subjects). The AUC of SVEAT score (0.8876, 95%CI: 0.82-0.96) was significantly higher than the AUC of HEART score (0.7962, 95%CI: 0.71-0.88), P = 0.03. Using logistic model, SVEAT score with cut-off of 4 or less significantly predicts 30-d MACE (odd ratio 1.52, 95%CI: 1.19-1.95, P = 0.001) but not the HEART score (odd ratio 1.29, 95%CI: 0.78-2.14, P = 0.32).

CONCLUSION

The SVEAT score is superior to the HEART score as a risk stratification tool for acute chest pain in low to intermediate risk patients.

Key Words: Acute chest pain; Risk stratification tool; Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin score; History, Electrocardiography, Age, Risk factors and Troponin score

Core Tip: Most chest pain risk stratification scores do not use several readily available data. The Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin (SVEAT) score was shown to outperform the History, Electrocardiography, Age, Risk factors and Troponin (HEART) score in 30-d major adverse cardiovascular event. In our retrospective cohort study, we validated the performance of the SVEAT score and confirmed that the SVEAT score is superior to the HEART score as a risk stratification tool for acute chest pain in low to intermediate risk patients.

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INTRODUCTION

Acute chest pain is one of the most common presenting symptoms to the emergency department[1,2]. Several non-cardiac conditions share clinical features with acute myocardial infarction and the emergency room clinician must rapidly identify those patients with chest pain who are most likely to have active coronary events from those who have chest pain due to other reasons. The key immediate task is to identify if a patient could benefit from being hospitalized for acute coronary syndrome (ACS) evaluation and those who can be safely discharged. This requires an estimation of the pretest probability of ACS. However, the accuracy of individual history, physical exam and electrocardiogram findings have been found to have limited utility for diagnosing ACS[3]. Therefore, multiple scoring systems and pathways have been proposed as risk stratification tools for these patients[4-7]. Among them, the History, Electrocardiography, Age, Risk factors and Troponin (HEART) score is arguably the most utilized particularly in the United States. Unfortunately, it has been shown in some studies to identify less than half of low-risk patients[4-6,8]. In an unselected population of chest pain patients in the emergency department, the HEART score and clinical gestalt had the same diagnostic accuracy for ACS[9]. The HEART score assigns a maximum score of 2 for chest pain deemed "highly suspicious" for ACS and suggests further inpatient evaluation for ACS for a score of 4 or more. By not clearly defining the classification of a patient's chest pain, the score introduces subjectivity and considerable inter-rater variability[10]. The score also incorporates traditional cardiac risk factors such as diabetes, hypercholesterolemia, and hypertension, which have been shown to have limited value in diagnosis ACS especially in those older than 40 years[11]. To control health care utilization and cost, it is imperative to identify low risk patients with chest pain for discharge from the emergency department. However, it is perhaps more important to not miss real cases of ACS in otherwise low risk patients. Among patients without the traditional risk factors for ACS, the HEART score may not be sensitive in identifying those who would benefit from further evaluation. Thus, there is a need for alternative risk stratification for this patient group. Recently, a new scoring system based on five sets of clinical variables; characteristics of chest pain Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin (SVEAT score, Table 1) has been reported to outperform the HEART score[8]. The objective of this study is to assess the potential usefulness of SVEAT score as a risk stratification tool by comparing its performance

Table 1 Definition of the Symptoms, History of Vascular disease, Electrocardiography, Age, and Troponin score

Component	Characteristics	Points
Symptoms	Typical unstable angina pectoris	3
	Stable angina, Canadian Cardiovascular Society Class I or II	1
	Non-cardiac chest pain	-2
Vascular disease	Recent myocardial infarction or percutaneous coronary intervention < 90 days	2
	Coronary artery bypass grafting > 5 years	2
	Prior coronary event other than above	1
	Prior revascularization for peripheral disease or carotid disease	2
EKG	Dynamic or new ischemic ST or T wave changes	3
	ST depression of unknown duration without cause	2
	ST changes with left ventricular hypertrophy, intraventricular conduction delay, digitalis, or metabolic issue	1
	Old Q wave indicating prior myocardial infarction or pre-existing ST changes	1
	No ST changes	0
	Normal EKG in the presence of severe ongoing chest pain	-2
Age (years)	> 75	2
	50-75	1
	30-49	0
	< 30	-1
Troponin I (ng/mL)	0.7 or higher	5
	> 0.12 but < 0.7	2
	> 0.04 but < or = 0.12	1
	Normal (< or = 0.004) with unclear duration of chest pain	0
	Normal after > 4 h of constant chest pain	-2

Reproduced from Roongsritong *et al*[8], 2020. With permission from Elsevier, Table 1 was reprinted from: Roongsritong C, Taha ME, Pisipati S, Aung S, Latt H, Thomas J, Namballa L, Al-Hasnawi HJ, Taylor MK, Gullapalli N. SVEAT Score, a Potential New and Improved Tool for Acute Chest Pain Risk Stratification. *Am J Cardiol* 2020; 127: 36-40. Copyright © 2020 Elsevier Inc.

to HEART score in chest pain patients with low suspicion for acute coronary syndrome and admitted for overnight observation.

MATERIALS AND METHODS

The registry of patients admitted to our clinical decision units between January 1st to April 17th, 2019, were retrospectively reviewed. Our clinical decision unit allows for close observation of chest pain patients who are at low risk for true major adverse cardiovascular event (MACE). Admission to this unit allows for serial monitoring of the patient's symptoms, cardiac enzymes, and electrocardiograms. To minimize any potential biases, one group of investigators was assigned to abstract relevant information necessary to calculate SVEAT score, and another was assigned to collect information for HEART score according to the published criteria[4,8]. The occurrence of MACE defined as all-cause mortality, acute myocardial infarction, confirmed coronary artery disease requiring revascularization or medical therapy at 30 d were then validated by two independent investigators who were blinded to the SVEAT and HEART score for each patient. The abstracted data were then provided to another set of investigators who were blinded to the outcome data to calculate the SVEAT and the HEART scores. Patients with ST segment elevation myocardial infraction were excluded from the study. The fourth-generation ultra-high sensitivity troponin I assay was used in all participants at our institution during the study period like the original SVEAT score study. Acute myocardial infarction was diagnosed based on standard

criteria[12]. The predictive power of the SVEAT and HEART scores for 30-d MACE were compared using c-statistic, based on area under the receiving-operator characteristic curve (AUC). Chi-squared test for equality of area under the curve was used to compare the performance of the SVEAT score to the HEART score. Categorical variables were summarized as counts (%) and between group comparisons were performed using Fisher's exact test. Continuous variables were summarized as means ± SD and difference between means by outcome compared using Student's *t*-test. All analyses were performed at a two-tailed 5% level of significance using Stata version 16.1 (Stata Corporation, College Station, TX, United States).

RESULTS

A total of 330 subjects were included in the study. Baseline patient characteristics are shown in Table 2. There were slightly more male (52.1%) than female subjects. The mean age was 59.5 ± 13.9 years. The incidence of 30-d MACE in our population was 3.33%. The subjects who suffered 30-d MACE were significantly older than those who did not (74.3 ± 13.2 years *vs* 59.0 ± 13.6 years, $P < 0.0001$). There were however no other significant differences in baseline characteristics between the two groups (Table 2).

Figure 1 illustrates the receiver-operator-characteristic curves of the SVEAT and HEART scores in predicting 30-d MACE. The AUC of the SVEAT score (0.8876, 95%CI: 0.82-0.96) is significantly higher than AUC of the HEART score (0.7962, 95%CI: 0.71-0.88), $P = 0.03$. Using logistic model, SVEAT score ≤ 4 significantly predicted 30-d MACE (odds ratio 1.52, 95%CI: 1.19-1.95, $P = 0.001$) but the HEART score ≤ 3 did not (odds ratio 1.29, 95%CI: 0.78-2.14, $P = 0.32$) (Table 3).

DISCUSSION

Currently, despite numerous risk stratification protocols, most low-risk patients presenting with acute chest pain are not being released from emergency department. The 2020 European Society of Cardiology Guideline for ACS recommends using an ultrahigh sensitivity troponin (hs-Tn) assay with 0/1-h hs-Tn protocol for ruling out acute coronary syndrome but also emphasizes the importance of incorporating clinical information into the decision-making process[12]. It additionally proposes using Global Registry of Acute Coronary Events score for prognostic purposes but does not recommend any specific clinical risk score for initial risk stratification[12]. The American College of Cardiology/American Heart Association has not updated their guideline since 2014 when they stated that none of available risk prediction tools at the time was definitively demonstrated to be superior to clinician judgement[13].

The HEART score is perhaps the most widely used risk stratification tool in the United States due to its simplicity and large amount of supporting evidence[6,14,15]. The criteria for its History and EKG component are however somewhat subjective. Consequently, inter-observer variability and scoring inconsistency have been reported[16-18]. More importantly, it has been shown to be able to identify merely less than half of low-risk patients[5,17,18]. One of the potential contributing factors for the latter issue is that the HEART score does not incorporate some of the useful clinical information readily available on initial evaluation. To circumvent some of the pitfalls of the HEART score, the SVEAT score was developed. There are a few differences between the SVEAT and HEART scores. First, larger weight (higher points) is assigned to the findings associated with higher likelihood of subsequent acute coronary event clinically and negative point for those traditionally associated with negative likelihood of the events in a stepwise manner. This approach allows wider range of potential scores, and we believe theoretically could help better discriminating among various risk group of patients. Secondly, the criteria for EKG changes and assigned point for each change are much more clearly defined. Moreover, the presence of vascular disease is included in the SVEAT score instead of risk factor which has been shown to be only a weak predictor in acute chest pain evaluation[19]. In fact, the SVEAT score has recently been shown to outperform the HEART score[8]. Like the previous study, this analysis found SVEAT score to be superior risk stratification tool to HEART score for acute chest pain evaluation in low-risk patients.

There are certainly a few limitations in our study. Firstly, the overall 30-d MACE incidence of 3.3% in this study is rather low and substantially lower than in the previous report of 19.6%[13]. This may unfavorably increase the possibility of our finding to be due to statistical chance. An extremely low event rate in this study is likely explained by our study design to include only those retrospectively identified from a low-risk chest pain registry at our institution. The incidence of MACE in our population however is in line with the recent report of real-world data in the United States where ED visit for acute chest pain exceeds 8 million annually[20]. Among these patients, < 5% of them subsequently experienced acute coronary syndrome. Second, the sample size of our study is relatively small for a retrospective design. As indicated in the methodology section, we did try to design our study to minimize potential biases. Lastly, this is a single center study and therefore future confirmation in a multicenter study in wider range of population, and larger sample size will be needed.

Table 2 Baseline patient characteristics

Continuous variables	Overall (*n* = 330)	30-d MACE		*P* value
		Yes, *n* = 11 (3.3%)	No, *n* = 319 (96.7%)	
Age, mean ± SD (yr)	59.5 ± 13.9	74.3 ± 13.2	59 ± 13.6	< 0.0001
BMI, mean ± SD (kg/m^2)	30.7 ± 7.8	27.8 ± 6.3	30.7 ± 7.8	0.23
Males, *n* (%)	172 (52.1)	7 (63.6)	165 (51.7)	0.55
Diabetes, *n* (%)	94 (28.5)	5 (45.5)	89 (27.9)	0.31
Dyslipidemia, *n* (%)	153 (46.4)	4 (36.4)	149 (46.7)	0.55
Hypertension, *n* (%)	206 (62.4)	10 (90.9)	196 (61.4)	0.06
Smoker, *n* (%)	177 (53.6)	9 (81.8)	168 (52.7)	0.07

Dyslipidemia: Total cholesterol > 200 mg/dL or low density lipoprotein > 130 mg/dL or non-high density lipoprotein cholesterol > 160 mg/dL. MACE: Major adverse cardiovascular events; BMI: Body mass index.

Table 3 Logistic model of major adverse cardiovascular events with HEART and SVEAT scores as covariates using cut-off of ≤ 4 points for SVEAT and ≤ 3 points for HEART for low-risk

30-d MACE	Odds ratio	*P* value	95%CI
HEART score	1.29	0.32	0.78-2.14
SVEAT score	1.52	0.001	1.19-1.95

MACE: Major adverse cardiovascular events; SVEAT: Symptoms, History of Vascular disease, Electrocardiography, Age, and Troponin; HEART: History, Electrocardiography, Age, Risk factors and Troponin.

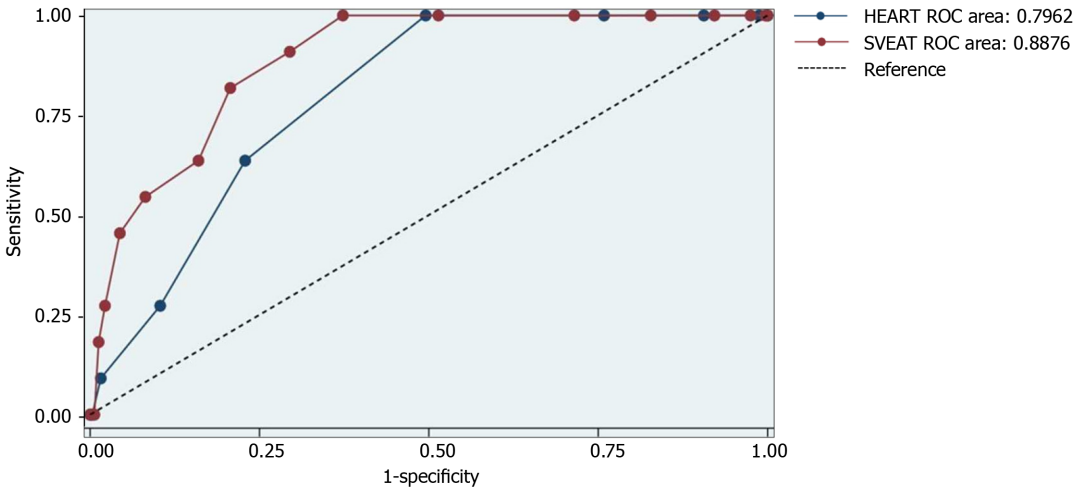

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Figure 1 Receiver operating characteristics for HEART and SVEAT scores. There area under the curve was significantly larger for SVEAT than HEART (*P* = 0.03). SVEAT: Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin; HEART: History, Electrocardiography, Age, Risk factors and Troponin; ROC: Receiver operating characteristics.

CONCLUSION

In conclusion, our study suggests potential usefulness of the newly developed SVEAT score as a risk stratification tool among low-risk patients admitted to clinical decision unit for evaluation of acute chest pain. We found that SVEAT score significantly outperforms the commonly used HEART score. Incorporating SVEAT score as part of a clinical assessment of these patients may help improve resource utilization while maintaining minimal risk of future cardiovascular events in low-risk patients presenting to emergency department with acute chest pain.

ARTICLE HIGHLIGHTS

Research background

Cardiovascular disease is the leading cause of death worldwide. Early identification of patients at risk for major cardiovascular events can expedite treatment and significantly reduce morbidity and mortality.

Research motivation

Risk stratification scoring systems used to identify patients at risk of major cardiovascular events, including the History, Electrocardiography, Age, Risk factors and Troponin (HEART) score, are often ineffective and may exclude many patients who would benefit from urgent intervention.

Research objectives

We aimed to assess the value of a new risk stratification scoring system, the Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin (SVEAT), by comparing its performance to that of the HEART score among chest pain patients with low suspicion for acute coronary syndrome.

Research methods

We retrospectively reviewed medical records of 330 consecutive patients admitted to our clinical decision unit for acute chest pain between January 1st to April 17th, 2019. To avoid potential biases, investigators assigned to calculate the SVEAT, and HEART scores were blinded to the results of 30-d combined endpoint of death, acute myocardial infarction or confirmed coronary artery disease required revascularization or medical therapy [30-d major adverse cardiovascular event (MACE)].

Research results

A 30-d MACE was observed in 11 patients (3.33% of the subjects). The area under receiving-operator characteristic curve (AUC) of SVEAT score (0.8876, 95%CI: 0.82-0.96) was significantly higher than the AUC of HEART score (0.7962, 95%CI: 0.71-0.88), P = 0.03. Using logistic model, SVEAT score with cut-off of 4 or less significantly predicts 30-d MACE (odd ratio 1.52, 95%CI: 1.19-1.95, P = 0.001) but not the HEART score (odd ratio 1.29, 95%CI: 0.78-2.14, P = 0.32).

Research conclusions

The SVEAT score is superior to the HEART score as a risk stratification tool for acute chest pain in low to intermediate risk patients.

Research perspectives

In our study, the SVEAT score was superior to the HEART score as a risk stratification tool for acute chest pain in low to intermediate risk patients. Future research is warranted to evaluate the SVEAT score among large, heterogeneous populations and among high-risk individuals presenting with chest pain.

FOOTNOTES

Author contributions: Antwi-Amoabeng D and Roongsritong C helped design the research study and wrote the original draft of the manuscript; Taha M, Beutler BD, Awad M and Hanfy A contributed to data curation, validation, and formal analysis; Ghuman J, Manasewitsch NT, Singh S and Quang C contributed to data curation and helped review and edit the manuscript; Gullapalli N supervised the project from initiation to completion.

Institutional review board statement: The study protocol was reviewed and approved by the University of Nevada, Reno School of Medicine Institutional Review Board.

Informed consent statement: The study was conducted in accordance with the policies of the Institutional Review Board of the University of Nevada, Reno School of Medicine. The trial was conducted as a retrospective cohort study using anonymized data from existing records. Therefore, informed consent was not required.

Conflict-of-interest statement: The authors declare no actual or potential conflicts of interest or relationship with industry.

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Cardiometabolic risk factors in young Indian men and their association with parameters of insulin resistance and beta-cell function

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Abstract

BACKGROUND

There is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia.

AIM

To evaluate young North Indian men (aged 20-50 years) for burden of cardiometabolic risk factors, in relation to parameters of homeostatic model assessment for insulin resistance (HOMA-IR) and beta-cell function (oral disposition index [oDI]).

METHODS

Study participants were invited in a fasting state. Sociodemographic, anthropometric, and medical data were collected, and 75 g oral glucose tolerance test was performed with serum insulin and plasma glucose estimation at 0, 30, and 120 min. Participants were divided into quartiles for HOMA-IR and oDI (category 1: Best HOMA-IR/oDI quartile; category 3: Worst HOMA-IR/oDI quartile) and composite HOMA-IR/oDI phenotypes (phenotype 1: Best quartile for both HOMA-IR and oDI; phenotype 4: Worst quartile for both HOMA-IR and oDI) were derived.

RESULTS

We evaluated a total of 635 men at a mean (± SD) age of 33.9 ± 5.1 years and body mass index of 26.0 ± 3.9 kg/m^2. Diabetes and prediabetes were present in 34 (5.4%) and 297 (46.8%) participants, respectively. Overweight/obesity, metabolic syndrome, and hypertension were present in 388 (61.1%), 258 (40.6%), and 123

(19.4%) participants, respectively. The prevalence of dysglycaemia, metabolic syndrome, and hypertension was significantly higher in participants belonging to the worst HOMA-IR and oDI quartiles, either alone (category 3 *vs* 1) or in combination (phenotype 4 *vs* 1). The adjusted odds ratios for dysglycaemia (6.5 to 7.0-fold), hypertension (2.9 to 3.6-fold), and metabolic syndrome (4.0 to 12.2-fold) were significantly higher in individuals in the worst quartile of HOMA-IR and oDI (category 3), compared to those in the best quartile (category 1). The adjusted odds ratios further increased to 21.1, 5.6, and 13.7, respectively, in individuals with the worst, compared to the best composite HOMA-IR/oDI phenotypes (phenotype 4 *vs* 1).

CONCLUSION

The burden of cardiometabolic risk factors is high among young Asian Indian men. Our findings highlight the importance of using parameters of insulin resistance and beta-cell function in phenotyping individuals for cardiometabolic risk.

Key Words: Cardiometabolic; Insulin resistance; Asian; Disposition index; Men; Young

Core Tip: There is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia. Against this backdrop, this study aimed to evaluate young North Indian men (aged 20-50 years) for: (1) Burden of glycemic and cardiometabolic traits; and (2) Their relation to parameters of insulin action and beta-cell function.

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INTRODUCTION

There is a huge burden of type 2 diabetes in South Asia. According to the latest International Diabetes Federation (IDF) estimates, 90 million adults suffer from diabetes in the South-East Asia region. These numbers are projected to increase to 113 million by 2030 and 152 million by 2045[1]. Several factors contribute to the diabetes epidemic in this region, with the prominent ones being increasing urbanisation and unhealthy changes in diet and lifestyle, reduced physical activity, unfavourable changes in leisure time activities, and decreasing sleeping quality and quantity[2]. Some predisposing factors integral to a "South Asian phenotype" also contribute. For instance, it has been found that despite a lower body mass index (BMI), Asian Indians develop diabetes at least a decade earlier, and are at a higher cardiovascular risk, compared to their Caucasian counterparts[3]. Existing data suggest significant beta cell dysfunction and insulin resistance (IR) in Asian Indians, even in the absence of diabetes[4]. This dual pathophysiological defect, manifested at a lower BMI and younger age, explains the huge burden of dysglycaemia in South Asians. Importantly, most studies on this subject were performed in a relatively older population (mean age in 40s or 50s), in those at high risk for diabetes, screened and selected for clinical trials, or in individuals of this ethnicity residing outside South Asia[5-8]. Thus, there is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia. Against this backdrop, this study aimed to evaluate young North Indian men (aged 20-50 years) for: (1) Burden of glycemic and cardiometabolic traits; and (2) Their relation to parameters of insulin action and beta-cell function.

MATERIALS AND METHODS

Settings and study design

This cross-sectional evaluation was performed from January 2016 to February 2020 at a tertiary care centre in North India (All India Institute of Medical Sciences, New Delhi). This is a post-hoc analysis of the data collected in two previously published studies that primarily evaluated the concordance of cardiometabolic risk factors among spouses of women with hyperglycaemia in pregnancy[9-10]. Both studies were approved by the institutional ethics committee, and written informed consent was obtained from all participants.

Inclusion and exclusion criteria

We included all men aged 20-50 years who participated in the aforementioned studies. For the purpose of this study, we excluded 20 participants who were diagnosed with diabetes requiring pharmacotherapy. Participants with missing blood insulin values (required to calculate IR and composite beta-cell function) were also excluded. The details of participant identification and recruitment have been provided earlier[9-10]. Briefly, participants were identified through their spouses and invited to visit the hospital, where study-related procedures (detailed below) were performed.

Procedure on the day of testing

Participants were invited to attend the hospital in a fasting state (minimum fast of 10 h) at 08:30 h. A detailed questionnaire was completed for each participant at the scheduled visit, documenting demographic details, education and employment status, and family history of diabetes mellitus.

Measurements

Weight, height, and waist circumference were recorded using standard methods (see supplementary material). A mean of three blood pressure readings was recorded. A 75 g oral glucose tolerance test with measurement of plasma glucose and serum insulin at 0, 30, and 120 min was performed using 83.3 g of glucose monohydrate (equivalent to 75 g anhydrous glucose) dissolved in 300 mL water and consumed over 5-10 min. Blood was also collected for a lipid profile and glycated hemoglobin (HbA_{1c}) measurement in the fasting state. The details of biochemical and hormonal measurements are provided in supplementary material.

Insulin index calculations

IR was measured by parameters of homeostatic model assessment for IR (HOMA-IR) using the standard formula [fasting plasma glucose (mmol/L) × fasting insulin (μIU/mL)/22.5]. Insulin secretion was measured by the insulinogenic index using the formula $\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30}$, and composite beta-cell function was measured by the oral disposition index using the formula: $\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30}$ X 1/fasting insulin (where $\Delta I_{0\text{-}30}$ is the change in serum insulin over 30 min [pmol/L] and $\Delta G_{0\text{-}30}$ is the change in plasma glucose over 30 min [mmol/L]). Negative insulinogenic and disposition index results because of a negative insulin or glucose response, and positive results from combined negative insulin and glucose responses were excluded[11].

Definitions of exposure variables

Participants were divided into quartiles for IR (HOMA-IR) and beta-cell function (oDI), based on which categories were defined[12]. Participants with values in the lowest (best) quartile (Q1 for HOMA-IR) and in the highest (best) (Q4 for oDI) were classified as the reference category (category 1). Participants in the worst or most affected quartile (Q4 for HOMA-IR and Q1 for oDI) were labelled as category 3. Participants with intermediate values (Q2/Q3 of HOMA-IR and oDI) were classified as category 2. Based on categories of HOMA-IR and oDI, composite IR/beta-cell function phenotypes were derived. Phenotype 1 was used as a reference category and included participants classified in category 1 (best quartile) for both HOMA-IR and oDI. Phenotype 4 was most severe, and included participants classified in category 3(worst quartile) for both HOMA-IR and oDI. Phenotype 3 included participants who had either HOMA-IR or oDI (not both) in category 3 (worst). All remaining participants were categorized as phenotype 2. These phenotypes and the categories based on HOMA-IR and oDI were used as exposure variables for the principal analysis, and cardiometabolic parameters were used as outcome variables.

Definitions of outcome variables

Individuals were classified as having normoglycaemia (fasting plasma glucose < 5.6 mmol/L, 2 h plasma glucose < 7.8 mmol/L, and HbA_{1c} < 39 mmol/mol [5.7%]), prediabetes (fasting plasma glucose 5.6-6.9 mmol/L and/or 2 h plasma glucose 7.8-11.0 mmol/L and/or HbA_{1c} 39-46 mmol/mol [5.7-6.4%]), or diabetes mellitus (fasting plasma glucose ≥ 7.0 mmol/L and/or 2 h plasma glucose ≥ 11.1 mmol/L and/or HbA_{1c} ≥ 48 mmol/mol [6.5%]) as per ADA criteria. Participants with prediabetes or diabetes were labelled as having dysglycaemia[13]. Metabolic syndrome was defined as per the IDF criteria: Waist circumference ≥ 90 cm, plus two of the following: Serum triglycerides ≥ 1.7 mmol/L, fasting plasma glucose ≥ 5.6 mmol/L, HDL-cholesterol < 1.03 mmol/L, and BP ≥ 130/85 mmHg[14]. Overweight and obesity were defined as BMI 25-29.9 and ≥ 30 kg/m^2, respectively (WHO international classification)[15]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or treatment with antihypertensive medications[16].

Statistical analysis

Statistical analyses were carried out using Stata 15.0 (Stata Corp, College Station, TX, United States). Data are presented as *n* (%), the mean ± SD, or median (q25-q75), as appropriate. Qualitative variables were compared between groups using the Pearson χ^2 test or Fisher's exact test. Quantitative variables were assessed for normality using the Shapiro-Wilk test. Variables with a normal distribution were

compared using Student's *t*-test for independent samples, and those that did not follow a normal distribution (*i.e.*, HOMA-IR, insulinogenic index, disposition index) were compared using the Wilcoxon rank-sum test. Logistic regression analysis was also used to evaluate the association of HOMA-IR, oDI, and mixed HOMA-IR/oDI categories with dysglycaemia, hypertension, and metabolic syndrome. The results are expressed as unadjusted and adjusted odds ratios (95% confidence interval [CI]). For adjusted analysis, the following covariates that are known to have a bearing on the outcome were accounted: Age and family history of diabetes (for dysglycaemia and metabolic syndrome), and age alone (for hypertension). The association of age and BMI with HOMA-IR and oDI was assessed using linear regression analysis. A P value of < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

We evaluated 635 men at a mean (± SD) age of 33.9 ± 5.1 years (range 21-49 years), and a mean (± SD) BMI of 26.0 ± 3.9 kg/m^2. Of the study participants, 312 (49.1%) and 76 (12.0%) were overweight and obese, respectively, and 245 (38.6%) had a family history of diabetes. Hypertension was present in 123 (19.4%) participants, and 19 (3.1%) were on pharmacotherapy. Diabetes and prediabetes were present in 34 (5.4%) and 297 (46.8%) participants, respectively. Metabolic syndrome was present in 258 (40.6%) participants. There were only 132 (20.8%) participants who did not have any adverse cardiometabolic risk factor, *i.e.*, dysglycaemia, hypertension, metabolic syndrome, and overweight/obesity. The results of various clinical, anthropometric, and biochemical variables are summarised in Table 1.

Burden of cardiometabolic risk factors in relation to age and body mass index

The prevalence of dysglycaemia increased with age, from 39.2% (in third decade) to 52.3% (in fourth decade) and to 68.0 % (in fifth decade) (P < 0.001). The corresponding figures for hypertension and metabolic syndrome were 12.0%, 18.7%, and 32.0%, respectively (P = 0.001), and 30.4%, 41.4% and 50.5%, respectively (P = 0.009). There was no significant HOMA-IR increment [beta coefficient 0.15 (P = 0.553) for 4th decade and 0.50 (P = 0.147) for 5th decade, compared to 3rd decade] and oDI decrement [beta coefficient: -0.59 (P = 0.137) for 4th decade and -1.00 (P = 0.057) for 5th decade, compared to 3rd decade] with age.

Similarly, the prevalence of dysglycaemia (34.8%, 60.3%, and 75.0%, respectively), hypertension (12.2%, 22.5%, and 30.3%, respectively), and metabolic syndrome (15.4%, 52.6%, and 73.7% respectively) increased across the three BMI categories, namely, normal weight, overweight, and obese (P < 0.001). HOMA-IR showed a significant increment across BMI categories [beta coefficient, adjusted for age: 1.34 (P < 0.001) for overweight and 3.37 (P < 0.001) for obese, compared to normal weight participants]. On the other hand, oDI showed a significant decrement across BMI categories [beta coefficient, adjusted for age: -1.38 (P < 0.001) for overweight and -1.58 (P = 0.002) for obese, compared to normal weight participants]

Cardiometabolic risk factors in relation to different IR (HOMA-IR) categories

We found a significantly higher burden of dysglycaemia (78.5% *vs* 34.8%, P < 0.001), hypertension (32.5% *vs* 12.0%, P < 0.001) and metabolic syndrome (66.5% *vs* 13.9%, P < 0.001) in participants belonging to the worst, compared to the best HOMA-IR quartile. The burden of adverse lipid parameters, *i.e.*, high total cholesterol (≥ 5.2 mmol/L; 39.5% *vs* 14.6%, P < 0.001), high LDL-cholesterol (≥ 2.6 mmol/L; 70.7% *vs* 38.0%, P < 0.001), high triacylglycerol (≥ 1.7 mmol/L; 58.0% *vs* 25.3%, P < 0.001), and low HDL-cholesterol (< 1.29 mmol/L; 61.8% *vs* 44.3%; P = 0.008), was also significantly higher in these participants (Table 2). The adjusted odds ratios (ORs) for dysglycaemia (OR = 7.04, 95%CI: 4.20-11.79; P < 0.001), hypertension (OR = 3.56, 95%CI: 1.97-6.43; P < 0.001), and metabolic syndrome (OR = 12.20, 95%CI: 6.91-21.54; P < 0.001) were significantly higher in participants belonging to quartile 4, compared to quartile 1 (Supplementary Table 1).

Cardiometabolic risk factors in relation to different composite beta-cell function (oral disposition index) categories

We found a significantly higher burden of dysglycaemia (80.4% *vs* 36.1%, P < 0.001), hypertension (30.6% *vs* 12.0%, P < 0.001), and metabolic syndrome (62.0% *vs* 26.6%, P < 0.001) in participants belonging to the worst, compared to the best oDI quartile. The burden of adverse lipid parameters, *i.e.*, high total cholesterol (≥ 5.2 mmol/L; 34.8% *vs* 20.3%, P = 0.005), high LDL-cholesterol (≥ 2.6 mmol/L; 65.2% *vs* 50.0%, P = 0.023), and high triacylglycerol(≥ 1.7 mmol/L; 57.6% *vs* 32.3%, P < 0.001), was also significantly higher in these participants (Table 3). The adjusted ORs for dysglycaemia (OR = 6.54, 95%CI: 3.90-10.97; P < 0.001), hypertension (OR = 2.89, 95%CI: 1.60-5.24; P < 0.001), and metabolic syndrome (OR = 4.02, 95%CI: 2.48-6.53; P < 0.001) were significantly higher in participants belonging to the worst, compared to the best quartile (Supplementary Table 2).

Table 1 Baseline characteristics of the study cohort

Variable	Total (*n* = 635)
Age (yr)	33.9 ± 5.1
Education (graduation or beyond)	373 (58.7)
Family H/O Diabetes	245(38.6)
BMI (kg/m^2)	26.0 ± 3.9
BMI ≥ 25 kg/m^2	388 (61.1)
BMI ≥ 30 kg/m^2	76 (12.0)
Waist circumference (cm) (*n* = 633)	94.1 ± 9.6
Waist circumference ≥ 90 cm	448 (70.8)
Systolic BP (mmHg) (*n* = 634)	122.2 ± 12.4
Systolic BP ≥ 140 mmHg	46 (7.3)
Diastolic BP (mmHg) (*n* = 634)	81.5 ± 9.6
Diastolic BP ≥ 90 mmHg	111 (17.5)
Hypertension	123(19.4)
Hypertension medications (*n* = 606)	19(3.1)
Total cholesterol (mmol/L) (*n* = 634)	4.7 ± 1.0
Total cholesterol ≥ 5.2 mmol/L	193 (30.4)
LDL-C (mmol/L) (*n* = 634)	2.9 ± 0.9
LDL-C ≥ 2.6 mmol/L	378 (59.6)
HDL-C (mmol/L) (*n* = 634)	1.0 ± 0.3
HDL-C < 1.03 mmol/L	336 (53.0)
Triacylglycerol (mmol/L) (*n* = 634)	1.6 (1.2-2.2)
Triacylglycerol ≥ 1.7 mmol/L	281 (44.3)
The metabolic syndrome	258 (40.6)
HOMA-IR (mmol/L × μIU/mL)	2.7 (1.9-4.0)
Matsuda index (*n* = 633)	2.8 (1.9-4.5)
Insulinogenic index ($pmol_{ins}/mmol_{glu}$)	203.2 (109.9-348.2)
Disposition index ($l/mmol_{glu}$)	2.6 (1.5-4.3)
Dysglycaemia	331 (52.1)
Prediabetes	297(46.8)
Diabetes	34(5.4)
Glucose at 0 min [mmol/L]	5.3 ± 1.2
Glucose at 30 min [mmol/L]	8.8 ± 2.3
Glucose at 120 min [mmol/L]	6.7 ± 2.8
HbA1c%	5.6 ± 0.8
HbA1c mmol/mol	38.1 ± 8.5
Insulin at 0 min [pmol/L]	84.5 (58.3-117.0)
Insulin at 30 min [pmol/L]	719.5 (438.1-1134.8)
Insulin at 120 min (*n* = 633) [pmol/L]	495.0 (257.2-861.9)
No risk factor	132 (20.8)

Data are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-

cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

Table 2 Comparison of cardiometabolic and glycaemic variables for men depending upon different categories of insulin resistance

Variable	Quartile 1 HOMA-IR < 25th percentile of total cohort *n* = 158	Quartile 2-3 HOMA-IR 25th to 75th percentile of total cohort *n* = 319	Quartile 4 HOMA-IR > 75th percentile of total cohort *n* = 158	*P* value[a]
Age (yr)	33.9 ± 5.0	33.8 ± 5.0	34.1 ± 5.2	0.775
Family H/O diabetes	45 (28.5)	124 (38.9)	76 (48.1)	0.002
BMI (kg/m^2)	23.3 ± 3.4	26.1 ± 3.2	28.5 ± 4.0	< 0.001
BMI ≥ 25 kg/m^2	53 (33.5)	204 (64.0)	131 (82.9)	< 0.001
Waist circumference (cm)	87.2 ± 8.9	94.4 ± 7.9	100.6 ± 9.0	< 0.001
Waist circumference ≥ 90 cm	66 (41.8)	239 (74.9)	143 (91.7)	< 0.001
Systolic BP ≥ 140 mmHg	7 (4.4)	18 (5.6)	21 (13.4)	0.003
Diastolic BP ≥ 90 mmHg	17 (10.8)	49 (15.4)	45 (28.7)	< 0.001
Hypertension	19 (12.0)	53 (16.6)	51 (32.5)	< 0.001
Total cholesterol ≥ 5.2 mmol/L	23 (14.6)	108 (33.9)	62 (39.5)	< 0.001
LDL-C ≥ 2.6 mmol/L	60 (38.0)	207 (64.9)	111 (70.7)	< 0.001
HDL-C < 1.03 mmol/L	70 (44.3)	169 (53.0)	97 (61.8)	0.008
Triacylglycerol ≥ 1.7 mmol/L	40 (25.3)	150 (47.0)	91 (58.0)	< 0.001
The metabolic syndrome	22 (13.9)	131 (41.1)	105 (66.5)	< 0.001
HOMA-IR (mmol/L × μIU/mL)	1.3 (1.0-1.6)	2.7 (2.3-3.2)	5.6 (4.6-7.3)	< 0.001
Insulinogenic index ($pmol_{ins}/mmol_{glu}$)	139.3 (85.0-218.0)	233.0 (136.4-362.0)	225.2 (99.8-425.7)	< 0.001
Disposition index ($l/mmol_{glu}$)	3.5 (2.2-5.8)	2.7 (1.6-4.1)	1.5 (0.7-2.6)	< 0.001
Dysglycaemia	55 (34.8)	152 (47.7)	124 (78.5)	< 0.001

[a]Data are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

Cardiometabolic risk factors in relation to phenotypes based on different combinations of HOMA-IR and oral disposition index

As mentioned in the methodology section, we evaluated the prevalence of cardiometabolic variables under four phenotypes based on different combinations of IR and beta-cell function (phenotype 4: Most affected; phenotype 1: Least affected). The burden of dysglycaemia (90.0% *vs* 28.4%; $P < 0.001$), hypertension (38.0% *vs* 9.0%; $P < 0.001$), and metabolic syndrome (70.0% *vs* 13.4%; $P < 0.001$) was significantly higher in phenotype 4 (oDI < 25th centile and HOMA-IR > 75th centile), compared to phenotype 1(oDI > 75th centile and HOMA-IR < 25th centile)). The burden of adverse lipid parameters, *i.e.* , high total cholesterol (≥ 5.2 mmol/L; 40.0% *vs* 14.9%, $P = 0.007$), high LDL-cholesterol (≥ 2.6 mmol/L; 73.8% *vs* 38.8%, $P < 0.001$), high triacylglycerol (≥ 1.7 mmol/L; 60.0% *vs* 19.4%, $P < 0.001$), and low HDL-cholesterol (< 1.03 mmol/L; 57.5% *vs* 49.3%; $P = 0.012$), was also significantly higher in these participants. These participants were also more likely to be overweight/obese (83.8% *vs* 29.9%; $P < 0.001$) and have central obesity (92.3% *vs* 35.8%; $P < 0.001$) (Table 4). The adjusted ORs for dysglycaemia (OR = 21.09, 95%CI: 8.47-52.53; $P < 0.001$), hypertension(OR = 5.60, 95%CI: 2.14-14.64; $P < 0.001$), and metabolic syndrome (OR = 13.65, 95%CI: 5.80-32.13; $P < 0.001$) were significantly higher in the participants belonging to phenotype 4, compared to phenotype 1 (Supplementary Table 3).

Table 3 Comparison of cardiometabolic and glycaemic variables for men depending upon different categories of beta-cell function (oral disposition index)

Variable	Quartile 4 oDI > 75th percentile of total cohort *n* = 158	Quartile 2-3 oDI 25th to 75th percentile of total cohort *n* = 319	Quartile 1 oDI < 25th percentile of total cohort *n* = 158	*P* value[a]
Age (yr)	33.1 ± 5.1	33.8 ± 4.9	35.0 ± 5.3	0.003
Family H/O diabetes	48 (30.4)	124 (38.9)	73 (46.2)	0.015
BMI (kg/m^2)	25.0 ± 3.9	25.9 ± 3.8	27.2 ± 3.7	< 0.001
BMI ≥ 25 kg/m^2	75 (47.5)	195 (61.1)	118 (74.7)	< 0.001
Waist circumference (cm)	91.8 ± 9.5	93.6 ± 9.5	97.6 ± 9.1	< 0.001
Waist circumference ≥ 90 cm	93 (58.9)	224 (70.2)	131 (84.0)	< 0.001
Systolic BP ≥ 140 mmHg	9 (5.7)	20 (6.3)	17 (10.8)	0.135
Diastolic BP ≥ 90 mmHg	15 (9.5)	53 (16.6)	43 (27.4)	< 0.001
Hypertension	19 (12.0)	56 (17.6)	48 (30.6)	< 0.001
Total cholesterol ≥ 5.2 mmol/L	32 (20.3)	106 (33.3)	55 (34.8)	0.005
LDL-C ≥ 2.6 mmol/L	79 (50.0)	196 (61.6)	103 (65.2)	0.013
HDL-C < 1.03 mmol/L	80 (50.6)	163 (51.3)	93 (58.9)	0.232
Triacylglycerol ≥ 1.7 mmol/L	51 (32.3)	139 (43.7)	91 (57.6)	< 0.001
The metabolic syndrome	42 (26.6)	118 (37.0)	98 (62.0)	< 0.001
HOMA-IR (mmol/L × μIU/mL)	2.1 (1.2-3.0)	2.6 (1.9-3.7)	4.0 (2.7-6.0)	< 0.001
Insulinogenic index ($pmol_{ins}/mmol_{glu}$)	410.5 (257.1-651.6)	215.6 (146.6-299.4)	85.6 (51.2-127.7)	< 0.001
Disposition index ($l/mmol_{glu}$)	6.1 (4.9-9.1)	2.6 (2.0-3.3)	0.8 (0.5-1.2)	< 0.001
Dysglycaemia	57 (36.1)	147 (46.1)	127 (80.4)	< 0.001

[a]Data are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

Odds ratio of dysglycaemia per SD change in HOMA-IR and oDI

On logistic regression analysis, the OR for dysglycaemia per SD increase in HOMA-IR was 3.22 (95%CI: 2.30-4.52; $P < 0.001$). After adjustment for age and family history of diabetes, the OR was 3.16 (95%CI: 2.24-4.47; $P < 0.001$). Similarly, the unadjusted and adjusted OR for dysglycaemia per SD decrease in oDI were 2.03 (95%CI: 1.60-2.59; $P < 0.001$) and 1.92 (95%CI: 1.51-2.44; $P < 0.001$), respectively.

DISCUSSION

We evaluated a large cohort of young Asian India men for the burden of cardiometabolic risk factors in relation to parameters of IR and beta-cell function. Apart from the traditional risk factors such as age and BMI, across which abnormal cardiometabolic traits increased, we found that individuals in the most severely affected quartiles of IR (HOMA-IR), beta-cell function (oDI), and a combination of both had a significantly higher burden of dysglycaemia, hypertension, metabolic syndrome, and adverse lipid parameters. These findings highlight the importance of using parameters of IR and beta-cell function in phenotyping individuals for cardiometabolic risk.

Our study cohort comprised of relatively young participants, with a mean age of ~34 years. Nearly one in two study participants had dysglycaemia, metabolic syndrome, or overweight/obesity, and every one in five participants had hypertension at such a young age. Previously, Staimez *et al*[5] reported a high dysglycaemia rate of 73% in 1264 individuals enrolled as a part of Diabetes Community Lifestyle Improvement Program in Chennai, India. The mean age and BMI were 44.2 years and 27.3 kg/m^2, respectively, compared to 33.9 years and 26.0 kg/m^2, in the current study; these differences

Table 4 Comparison of cardiometabolic and glycaemic variables for men depending upon different categories based on beta-cell function (oral disposition index) and insulin resistance

Variable	Phenotype 1 oDI > 75th and HOMA-IR < 25th percentile of total cohort *n* = 67	Phenotype 2 oDI 25th to 75th and/or HOMA-IR 25th to 75th percentile of total cohort *n* = 332	Phenotype 3 oDI < 25th or HOMA-IR > 75th percentile of total cohort *n* = 156	Phenotype 4 oDI < 25th and HOMA-IR > 75th percentile of total cohort *n* = 80	*P* value[a]
Age (yr)	33.3 ± 4.5	33.7 ± 5.1	34.0 ± 5.2	35.1 ± 5.3	0.096
Family H/O diabetes	18 (26.9)	113 (34.0)	79 (50.6)	35 (43.8)	0.001
BMI (kg/m^2)	23.2 ± 3.3	25.4 ± 3.5	27.1 ± 3.6	28.5 ± 4.0	< 0.001
BMI ≥ 25 kg/m^2	20 (29.9)	186 (56.0)	115 (73.7)	67 (83.8)	< 0.001
Waist circumference (cm)	86.9 ± 8.4	92.5 ± 8.9	97.2 ± 8.7	101.0 ± 9.1	< 0.001
Waist circumference ≥ 90 cm	24 (35.8)	222 (66.9)	130 (83.3)	72 (92.3)	< 0.001
Systolic BP ≥ 140 mmHg	3 (4.5)	18 (5.4)	12 (7.7)	13 (16.5)	0.014
Diastolic BP ≥ 90 mmHg	4 (6.0)	45 (13.6)	36 (23.1)	26 (32.9)	< 0.001
Hypertension	6 (9.0)	48 (14.5)	39 (25.0)	30 (38.0)	< 0.001
Total cholesterol ≥ 5.2 mmol/L	10 (14.9)	98 (29.5)	53 (34.2)	32 (40.0)	0.007
LDL-C ≥ 2.6 mmol/L	26 (38.8)	197 (59.3)	96 (61.9)	59 (73.8)	< 0.001
HDL-C < 1.29 mmol/L	33 (49.3)	159 (47.9)	98 (63.2)	46 (57.5)	0.012
Triacylglycerol ≥ 1.7 mmol/L	13 (19.4)	134 (40.4)	86 (55.5)	48 (60.0)	< 0.001
The metabolic syndrome	9 (13.4)	102 (30.7)	91 (58.3)	56 (70.0)	< 0.001
HOMA-IR (mmol/L × μIU/mL)	1.1 (0.7-1.5)	2.4 (1.9-3.0)	4.0 (2.7-5.0)	5.9 (4.7-8.8)	< 0.001
Insulinogenic index ($pmol_{ins}/mmol_{glu}$)	237.4 (156.4-377.1)	228.6 (147.9-348.5)	159.0 (72.8-418.7)	99.9 (57.3-166.1)	< 0.001
Disposition index ($l/mmol_{glu}$)	6.5 (5.1-9.4)	3.0 (2.3-4.1)	1.5 (1.0-2.6)	0.7 (0.3-1.1)	< 0.001
Dysglycaemia	19 (28.4)	133 (40.1)	107 (68.6)	72 (90.0)	< 0.001

[a]Data are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

explain the higher burden of dysglycaemia in the former study, compared to ours. In a similar vein, we also found that the burden of various risk factors increased across age and BMI, being higher in individuals in the fourth and fifth decades of life, and in those with overweight/obesity. The mean HOMA-IR (mmol/L × μIU/mL) in the former study was 2.9, compared to 2.7 in the current study. Notably, we found that mean HOMA-IR in participants in the fifth decade of life (who also had a comparable BMI of 26.9 kg/m^2) was strikingly similar at 2.9. This highlights the convergence of phenotype in terms of obesity and IR, in two studies performed in geographically diverse regions of the country, and lends credibility to generalisation of our study findings to a wider population base.

Both IR and beta cell dysfunction contribute to the pathophysiology of diabetes, and the relative contribution of the latter is proposed to be higher in South Asians[4-6]. In fact, early beta cell dysfunction has been reported not only in Native Asian Indians, but also in migrant populations. The MASALA study found that after adjusting for visceral adiposity and other risk factors, oDI, not Matsuda index, was associated significantly with prediabetes and diabetes among migrant Asian Indians in the United States[6]. Previously, an Iranian study found that HOMA-IR is significantly associated with hypertension in subjects with and without diabetes[17]. We investigated whether and to

what extent the burden of cardiometabolic risk factors varies across severity of HOMA-IR (a parameter of IR) and oDI (a parameter of composite beta-cell function), individually and in combination. The prevalence of dysglycaemia was especially high in participants belonging to the worst HOMA-IR (78.5%) and oDI (80.4%) quartile. Further, the prevalence was 90.0% in participants who had both HOMA-IR and oDI in the worst quartile, compared to 28.4% in those with both indices in the best quartile. We also found that the adjusted ORs for dysglycaemia (6.5 to 7.0-fold), hypertension (2.9 to 3.6-fold), and metabolic syndrome (4.0 to 12.2-fold) were significantly higher in individuals in the worst quartile of HOMA-IR and oDI, compared to those in the best quartile. When accounting for individuals with the worst, compared to those with the best HOMA-IR and oDI combined, the corresponding adjusted ORs further increased to 21.1, 5.6, and 13.7, respectively. Our study findings are in line with those reported in a recent cross-sectional study by Wang *et al*, where authors found that the prevalence of various cardiometabolic risk factors increased across quintiles of HOMA-IR and HOMA-B in Chinese adults (n = 93690)[18]. Compared to this study, we used oDI as a marker of composite beta-cell function, since it corresponds to biological definition of beta-cell function, in the sense that insulin secretion (Δ I0-30/ Δ G0-30) is measured in relation to existing insulin sensitivity(1/fasting insulin), and is also known to predict the development of future diabetes[19].

The strengths of our study are a comprehensive evaluation of cardiometabolic risk in a cohort of young Indian men, and reporting of data in relation to parameters of IR and beta-cell function, both relevant to the pathophysiology of diabetes. We used oDI to measure beta-cell function, compared to other more extensive studies that used HOMA-B[12]. Our study findings add to the limited and evolving understanding of diabetes pathophysiology in South Asians. We acknowledge certain limitations of this work. Our study provides a cross-sectional association between cardiometabolic risk factors and parameters of insulin action/beta-cell function; however, causality cannot be ascertained. We did not evaluate the study participants for cardiovascular complications such as coronary artery disease and peripheral vascular disease. However, it may be too early for these complications to manifest in this young cohort. In this regard, it would be of interest to follow this cohort longitudinally and evaluate incident glycemic and cardiometabolic deterioration, and development of cardiovascular complications, based on baseline quartiles of oDI and HOMA-IR.

CONCLUSION

To conclude, the burden of cardiometabolic risk factors is high among young Asian Indian men, and both IR and beta cell dysfunction contribute to the pathophysiology of dysglycaemia in this population. Future longitudinal studies should evaluate incident cardiometabolic risk among individuals profiled at baseline for these insulin parameters, and suggest strategies to mitigate the increased risk.

ARTICLE HIGHLIGHTS

Research background

Existing data suggest significant beta cell dysfunction and insulin resistance (IR) in Asian Indians, even in the absence of diabetes. This dual pathophysiological defect, manifested at a lower body mass index (BMI) and younger age, explains the huge burden of dysglycaemia in South Asians. Importantly, most studies on this subject were performed in a relatively older population (mean age in 40s or 50s), in those at high risk for diabetes, screened and selected for clinical trials, or in individuals of this ethnicity residing outside South Asia. Thus, there is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia.

Research motivation

There is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia.

Research objectives

To evaluate young North Indian men (aged 20-50 years) for: (1) Burden of glycemic and cardiometabolic traits; and (2) Their relation to parameters of insulin action and beta-cell function.

Research methods

Study participants were invited in a fasting state. Sociodemographic, anthropometric, and medical data were collected, and 75 g oral glucose tolerance test was performed with serum insulin and plasma glucose estimation at 0, 30, and 120 min. Participants were divided into quartiles for homeostatic model assessment for IR (HOMA-IR) and oDI (category 1: Best HOMA-IR/oDI quartile; category 3: Worst HOMA-IR/oDI quartile) and composite HOMA-IR/oDI phenotypes (phenotype 1: Best quartile for

both HOMA-IR and oDI; phenotype 4: Worst quartile for both HOMA-IR and oDI) were derived.

Research results

We evaluated a total of 635 men at a mean (± SD) age of 33.9 ± 5.1 years and BMI of 26.0 ± 3.9 kg/m^2. Diabetes and prediabetes were present in 34 (5.4%) and 297 (46.8%) participants, respectively. Overweight/obesity, metabolic syndrome, and hypertension were present in 388 (61.1%), 258 (40.6%), and 123 (19.4%) participants, respectively. The prevalence of dysglycaemia, metabolic syndrome, and hypertension was significantly higher in participants belonging to the worst HOMA-IR and oDI quartiles, either alone (category 3 *vs* 1) or in combination (phenotype 4 *vs* 1). The adjusted odds ratios for dysglycaemia (6.5 to 7.0-fold), hypertension (2.9 to 3.6-fold), and metabolic syndrome (4.0 to 12.2-fold) were significantly higher in individuals in the worst quartile of HOMA-IR and oDI (category 3), compared to those in the best quartile (category 1). The adjusted odds ratios further increased to 21.1, 5.6, and 13.7, respectively, in individuals with the worst, compared to the best composite HOMA-IR/oDI phenotypes (phenotype 4 *vs* 1).

Research conclusions

The burden of cardiometabolic risk factors is high among young Asian Indian men. Our findings highlight the importance of using parameters of IR and beta-cell function in phenotyping individuals for cardiometabolic risk.

Research perspectives

We evaluated a large cohort of young Asian India men for the burden of cardiometabolic risk factors in relation to parameters of IR and beta-cell function. Apart from the traditional risk factors such as age and BMI, across which abnormal cardiometabolic traits increased, we found that individuals in the most severely affected quartiles of IR (HOMA-IR), beta-cell function (oDI), and a combination of both had a significantly higher burden of dysglycaemia, hypertension, metabolic syndrome, and adverse lipid parameters. These findings highlight the importance of using parameters of IR and beta-cell function in phenotyping individuals for cardiometabolic risk.

FOOTNOTES

Author contributions: Gupta Y conceived the idea and wrote the manuscript; Goyal A, Kalaivani M, and Tandon N read and edited the manuscript; Kalaivani M did the statistical analysis; all authors approved the final version of this manuscript.

Institutional review board statement: This is a post-hoc analysis of the data collected in two previously published studies that primarily evaluated the concordance of cardiometabolic risk factors among spouses of women with hyperglycaemia in pregnancy. Both studies were approved by the institutional ethics committee, and written informed consent was obtained from all participants.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Yashdeep Gupta, Alpesh Goyal, Mani Kalaivani, and Nikhil Tandon have nothing to disclose for this article.

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