

Review article

Preoperative glycosylated hemoglobin concentration and early postoperative infections in patients undergoing spinal surgery: A systematic review

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ABSTRACT

Early postoperative infections can affect a significant number of spinal surgery patients. Many studies reported on the features that may associate with elevated risk of infectious complications in this group. Data on the impact of glucose metabolism disorders in this area are well known. At the same time information on the correlation of preoperative HbA1c level and postoperative infections in spinal surgery are still scarce. Furthermore there are no strict recommendations regarding routine HbA1c testing prior to elective surgery. In present SR we aimed to report available clinical evidence on association between preoperative HbA1c and early postoperative infections. We used PubMed and EMBASE database and a set of specific key words (spine surgery AND infections AND HbA1c) to identify eligible studies. The study was registered in PROSPERO database and reported according to PRISMA recommendations. 16 studies were selected for further assessment. Predominance of data indicated a significant correlation between preoperative HbA1c concentration and elevated risk of postoperative infections, as well as higher rate of non - infective complications and worse patients future outcome. Adequately designed future studies on purposely dimensioned sample size are needed to confirm the role of preoperative HbA1c testing in preoperative management of spinal surgery patients.

1. Introduction

Spinal surgery (SS) associates with early postoperative complications occurring in 4–16.4% of patients.[1,2] These include surgical, medical and neurological complications.[3] Early postoperative infections can complicate up to 9% of the cases [4] and implicate the need for revision surgeries, long - term use of intravenous antibiotics and finally - prolonged hospitalization resulting in higher economic costs. Infection rates may vary depending on the type and extent of surgery, use of instrumentation and patient's characteristics.[5] Increased incidence of postoperative infections is reported in patients with a chronic state of impaired glucose metabolism.[6] Infectious complications may present as local site infections with a diverse degree of severity (surgical site infections (SSI) - either superficial or deep subfascial infections with myonecrosis) as well as systemic infections such as pneumonia, urinary tract infection (UTI) or sepsis [7].

Several preoperative risk factors that can correlate with postoperative infections have been identified. These include anemia, body mass index, coexistent infection at a remote site, the use of steroids and

diabetes mellitus (DM).[8–10] It is not clear if and to which extent elevated glycosylated hemoglobin (HbA1c) concentration is a preoperative risk factor for patients undergoing SS. Several clinical studies in various surgical settings have reported a relationship between HbA1c and an increased risk for postoperative infections.[11–13].

No dedicated systematic reviews (SR) have addressed the issue on the possible role of HbA1c as predictor of early postoperative infections in patients undergoing elective spine surgery procedures.

Aim of this SR is to report available clinical evidence on the relationship between increased preoperative HbA1c and early postoperative infections in patients undergoing spinal surgery.

2. Materials and methods

A detailed systematic search of database resources (PubMed and EMBASE) was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement recommendations. The study was registered in the International Prospective Register of Systematic Review (PROSPERO) database (registration

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The following keywords were used: spine surgery AND infections AND HbA1c. Applied filters were: studies published between January 2000 and March 2023, full-length articles (no abstracts), human adult population (older than 18 years) and English language. Literature search included references from original articles. Duplicates were eliminated. Randomized controlled trials, prospective and retrospective observational studies and case series including more than 5 patients that reported the association between preoperative HbA1c concentration and the incidence of postoperative infections qualified for the present SR. Data extraction included additional reported outcomes associated with elevated HbA1c as well as significant features correlated with the incidence of infectious and non-infectious complications in patients undergoing SS.(Table 1.) Case reports, case report series (with less than 5 cases), systematic reviews and meta-analyses were excluded from the search. We also excluded the studies on pediatric population.

3. Results

PubMed and EMBASE search led to 580 matching articles. After screening for eligibility 564 articles were excluded as they did not match the inclusion criteria.(Fig. 1) A total of 16 studies were assessed as suitable for the present SR (2 prospective observational studies and 14 retrospective observational studies), which included a total of 112 906 patients, who underwent spinal surgical procedures. 15 of the studies selected as appropriate for the present SR exclusively recruited patients who had undergone SS, one study included a wider group of surgical patients with a specified subgroup of spinal procedures (only data related to the latter group were analyzed in this SR).

All of the selected studies reported data on the relationship between HbA1c and postoperative infection incidence. Additional outcome measures listed in the included studies were: early postoperative non-infective complications [15–20,27] functional outcome [15,20,27] and postoperative follow up features such as length of hospitalization [18,20,24], need for re-admission and re-operation [15,20,27], 30-day morbidity and 90-day mortality [16].

Extracted and analyzed data from the selected studies are presented according to numerosity of recruited patients and the type of reported outcome in following order: postoperative infections, non-infective postoperative complications, postoperative functional outcome and postoperative follow-up.

3.1. Relationship between HbA1c and postoperative infections

The 16 selected studies consistently reported on a relationship between HbA1c and postoperative infections. In included studies postoperative infections were identified with the use of common procedure terminology (CPT) codes or International Classification of Diseases (ICD) codes and defined as SSI, wound complications, organ infections: pneumonia, UTI and generalised infections (sepsis). Follow-up period in analyzed studies ranged from 30 days [19,22,24] up to 12 months after the procedure.[15,18,21,23,25,28,30].

In 10 of the selected studies [17,19–21,23–26,28,30] including a total number of 110 453 subjects a significant positive association between postoperative infection rates and elevated preoperative HbA1c was reported. Not all of them defined the precise HbA1c threshold above which the risk of postoperative infections in spinal surgery patients may increase. Six of the analysed studies (4 retrospective observational and 2 prospective studies) investigating a total number of 2898 subjects reported no significant association between postoperative infection rates and HbA1c.[15,16,18,22,27,29].

In three retrospective observational studies [23,25,30] including a total of 9058 patients the HbA1c threshold above which the risk of postoperative infections increased was specified as 7.5%. The reported absolute infection rates in patients with HbA1c > 7.5% were significantly higher than in a group with HbA1c < 7.5%. In other studies the

cut off values of HbA1c indicating a higher risk of postoperative infections varied from 6.65% [19] to 8%.[20].

3.2. Relationship between HbA1c and non-infective postoperative complications

In 7 of the selected studies (5 retrospective studies, one prospective cohort study and one prospective single center study) that included 53473 patients non-infective postoperative complications diagnosed during hospitalization and within 90 days of surgery were recorded. [15–20,27] The reported non-infective complications included: neurological (new neurologic deficit); cardiac (arrhythmia, myocardial infarction, congestive cardiac failure and cardiac arrest); pulmonary (respiratory arrest and acute respiratory disease syndrome); renal (acute renal failure) and thrombo-embolic (deep vein thrombosis and pulmonary embolism, disseminated intravascular coagulation).

In four retrospective cohort studies investigating a total of 51766 subjects the correlation between HbA1c and incidence of postoperative complications was confirmed.[15,17,19,20].

Three of the analysed studies [16,18,27] including 1707 subjects failed to show a significant association between preoperative HbA1c level and the rate of postoperative complications.

3.3. Relationship between HbA1c and postoperative functional outcome

In 3 studies that included a total of 5363 patients authors reported evidence on the relationship between elevated preoperative HbA1c and postoperative functional outcome with conflicting results.[15,20,27].

Two retrospective studies [20,27] investigating a total of 4955 subjects proved that patients undergoing spinal surgery with elevated preoperative HbA1c were less likely to achieve functional improvement in the 90-day follow up period. The threshold for preoperative HbA1c predisposing for worse functional outcome was defined as > 7.8% [27] and > 8% [20] respectively.

In a retrospective observational study on a group of 408 patients [15] no association was found between preoperative HbA1c and minimum clinically important difference in NRS-Neck pain as well as NRS-Arm pain on 3 month and 12 month follow up.

3.4. Relationship between HbA1c and postoperative follow up

In three studies investigating 5310 patients [18,20,24] elevated HbA1c was a predictor of longer hospital stay after undergoing spinal intervention. The re-admission and re-operation rate was reported in three retrospective studies [15,20,27] on a total number of 5363 subjects. Significantly higher risk for re-admission and re-operation associated with preoperative HbA1c > 8% was reported in a large, retrospective study on 4778 subjects.[18] No correlation between HbA1c and re-admission and re-operation rate was found in two retrospective studies including a total of 585 patients.[15,27].

The 30-day morbidity and 90-day mortality was reported in one of the selected studies including 1090 spinal surgery patients.[16] No significant correlation between preoperative HbA1c level and increased 30-day morbidity and 90-day mortality rates were confirmed.

4. Discussion

This SR originally reports data on the relationship between preoperative HbA1c and the incidence of postoperative infections in patients undergoing SS. In majority of selected studies, the elevated preoperative HbA1c associated with higher risk of postoperative infections (especially SSI's) as well as non-infectious postoperative complications including: thrombotic events, acute kidney injury, delirium or anemia requiring transfusion. Patients with elevated HbA1c were also less likely to achieve functional improvement after the treatment and demonstrated higher incidence of re-admissions and the need for re-operation.

Table 1
Summary of the research included in the systematic review.

Authors, year	Study design	Study group (n)	Patients characteristics	Primary outcome	Secondary outcome	HbA1C threshold	Results	Follow up period
Roth, 2022	Retrospective cohort study	408	DM patients, 259 ACF 149 PCLF	NRS - Arm pain. NDI	SSI, Complications. Reoperations. Readmissions.	6.8%	HbA1c levels above 6.8% related to worse outcomes, but not specifically associated with infections (SSI, urinary, pneumonia)	3 m, 12 m 90 days
Lam; 2022	Prospective cohort study	1090	Spinal surgery patients	Postoperative complications including infections	30 day morbidity 90 day morbidity	Not specified	No significant correlation between complications rate in spinal surgery patients with elevated HbA1c	30 days 90 days
Zhuang, 2019	Retrospective cohort study	46490	DM patients undergoing PLF with instrumentation	Incidence of SSI, divided into superficial and deep	Secondary complications: incidence of CVE, AKI, PE, pneumonia, UTI, blood transfusion	Not specified	HbA1c was associated with elevated risk of deep SSI, pneumonia, UTI, as well as other complications	90 days
Tanaka; 2021	Single centre prospective study	440	Patients undergoing spinal surgery	Postoperative complications including infections		< 5.7% 5.7–6.4% 6.5–7.9% > 8%	No significant correlation between SSI rate and HbA1c	2weeks, 3 m, 6 m, 9 m, 12 m
Kiridly, 2020	Retrospective cohort study	90	Patients undergoing elective lumbar spinal fusion	Postoperative complications including infections	Not specified	6.65%	Higher mean HbA1c levels (6.82 vs 7.58, p = 0.033) in a group with complications; HbA1c level most predictive of postoperative complications within 30 days was 6.65%	30 days
Lim , 2021	Retrospective cohort study	4778	Elective lumbar surgeries	Postop complications (including SSI)	Readmissions (30RA, 90RA); LOH; Patients satisfaction; Functional improvement (MCID)	> 8%	HbA1c > 8% were more likely to experience postoperative complications, extended LOH and are less likely to achieve functional improvement	90 days
Hikata, 2014	Retrospective cohort study	445	Patients undergoing posterior instrumented thoracic and lumbar spinal arthrodesis 36 DM 309 non-DM	SSI rate	Nor specified	> 7%	Higher rate of SSI in DM patients; higher value of HbA1c in patients who developed SSI (7.6%); SSI developed in 0% patients with HbA1c < 7% and in 35.3% pt with HbA1c > 7%	12 m
Satake, 2013	Retrospective cohort study	110	DM patients who underwent spinal instrumentation surgery, 11 developed SSI 99 nonSSI	Identifying factors predisposing to SSI	Nor specified	Not specified	No significant difference of preoperative HbA1c and serum glucose level in SSI and non-SSI patients	30 days
Peng, 2019	Retrospective cohort study	523	DM patients who underwent posterior lumbar surgery	Correlation of HbA1c and other factors (sex, age, BMI, smoking, new DM, Alb, FBG, PBG, segment, operation time, blood loss, local fat thickness and incision infection rate	Nor specified	7.5%	Preoperative HbA1c $\geq 7.50\%$ was significantly correlated with incision infection rate	30 day - 12 m
Hwang, 2019	Retrospective cohort study	92	Single-level lumbar posterior fusion 24 SSI 68 noSSI	Level of HbA1c	LOH	6.9%	HbA1c levels were significantly higher in patients with SSI (6.78%) than those without (5.99%) HbA1c for elevated risk of SSI was $\geq 6.9\%$	30 days

(continued on next page)

Table 1 (continued)

Authors, year	Study design	Study group (n)	Patients characteristics	Primary outcome	Secondary outcome	HbA1c threshold	Results	Follow up period
Cancienne, 2017	Retrospective case control database study	5194	DM patients who underwent single - level lumbar decompression	Incidence of deep infections requiring operative intervention within 1 year	Threshold of HbA1c above which the risk increases	7.5%	HbA1c > 7.5% correlates with significantly higher risk for deep infection	12 m
Ross, 2021	Retrospective, nonrandomised database study	49271	Patients undergoing elective surgery for degenerative spine conditions 2941 inf (6%)	Wound infection rate	No	Not specified	HbA1c is a significant predictor of infection with an odds ratio of 1.042 for each 1% increase in the test result; Age and BMI are also associated with the risk of infection	6 m
Gupta, 2022	Single-center, retrospective cohort study	177	1819 spinal 177 had HbA1c	The rate of SSI PRO's (NRS, ODI)	Complications Readmissions Reoperations	7.5%	HbA1c > 7.8% associated with higher NRS-Back pain MCID30 HbA1c> 7.5% associated with higher ODI MCID30 No significant association between HbA1c and SSI (SSI in 1.7% patients only)	90 days
Patel, 2021	Single-center retrospective cohort study	229	DM patients undergoing posterior spinal fusion	Association between HbA1c and WC and PA	Association between WC and PA and patient features (osteopenia, BMI, LF)	7.05%	HbA1c > 7.05%, is a predictor of postoperative wound complications	12 m
O'Malley, 2022	Retrospective cohort study	228	DM patients who underwent thoracic, lumbar, or thoracolumbar posterior spinal fusion	WC rate - dehiscence, superficial SSI and deep SSI.	Identifying factors predisposing to WC	Not specified	No correlation between postoperative WC and preoperative HbA1c	Not specified
Cancienne, 2017	Retrospective case control database study	3341	DM patients who underwent primary anterior cervical discectomy and fusion	Incidence of infections requiring operative intervention within 1 year	Threshold of HbA1c above which the risk increases	7.5%	HbA1c > 7.5% correlates with significantly higher risk for deep infection	12 m

DM - diabetes mellitus, ACF- anterior cervical fusion, PCLF - posterior cervical laminectomy and fusion, NRS - numeric rating scale, NDI - neck disability index, SSI - surgical site infection, HbA1c - glycated hemoglobin, PLF - posterior lumbar fusion, UTI - urinary tract infection, CVE - cerebrovascular event, PE - pulmonary embolism, AKI - acute kidney injury, LOH - length of hospitalisation, MCID - minimal clinically important difference, BMI - body mass index, FBG - fasting blood glucose, PGB- postprandial blood glucose, WC - wound complications, PA - pseudoarthrosis, LF - levels fused, PRO's - patient reported outcomes, ODI - Oswestry Disability Index, RA - readmission

The data on the positive association between HbA1c and the incidence of postoperative infections was reported in previous studies addressing the problem of preoperative glycemic control in patients undergoing various surgical procedures. A recent SR stated, that HbA1c > 8% correlates with higher risk of complications following the treatment. Infections associated with elevated HbA1c and its level in patients experiencing SSI was higher by 1.49% comparing to controls.[31] Another SR analysing a predictive value of preoperative assessment of hemoglobin, hematocrit and HbA1c in a group of SS patients revealed that HbA1c is predictive of postoperative infection and functional outcomes.[32] In both mentioned SR's however HbA1c is analysed as one of possible factors for postoperative complications. The methodological design of studies included in previous reviews does not specify postoperative infections as a main outcome and analyses many risk factors for postoperative complications. To investigate the indications for preoperative HbA1c testing in SS patients the design of studies should concentrate on infectious sequelae as a primary outcome in a specified group of spinal procedures.

Optimising glucose metabolism should be pursued during all of the stages of preoperative period. Recent studies on a group of neurosurgery and orthopaedic patients [33,34] state, that proper management of intraoperative and postoperative hyperglycemia could also be beneficial

in reducing the incidence of postoperative infections, however it is suggested, that chronic glucose metabolism disorders might be a more significant risk factor than acute episodes of hyperglycemia.[34].

Studies included in present SR did not provide a consequent HbA1c threshold associated with elevated risk of postoperative infections as well as non-infectious complications in SS patients. The American Diabetes Association guidelines recommend maintaining HbA1c levels in DM patients below 7.0% prior to elective surgery to minimize the incidence of complications.[35] In present SR the level above which a risk of postoperative infections differed between the studies and was reported as 6,65% [19] up to 8%.[22] In a large number of studies the exact threshold was not specified at all.[16,17,22,26,29] Recommendations presented in SR by Haropp state, that in all DM patients qualified for SS preoperative HbA1c testing should be performed.[36] It is additionally recommended that these individuals should be consulted before the surgery regarding the increased risk of preoperative complications if the HbA1c level exceeds 7.5%.

Numerous studies have analyzed, how improving preoperative patients management can reduce the complication rate in patients undergoing SS procedures.[37] Efforts have been made to stratify the risk of postoperative infectious complications in SS based on patients features and comorbidity.[38] A recent study aimed to develop a

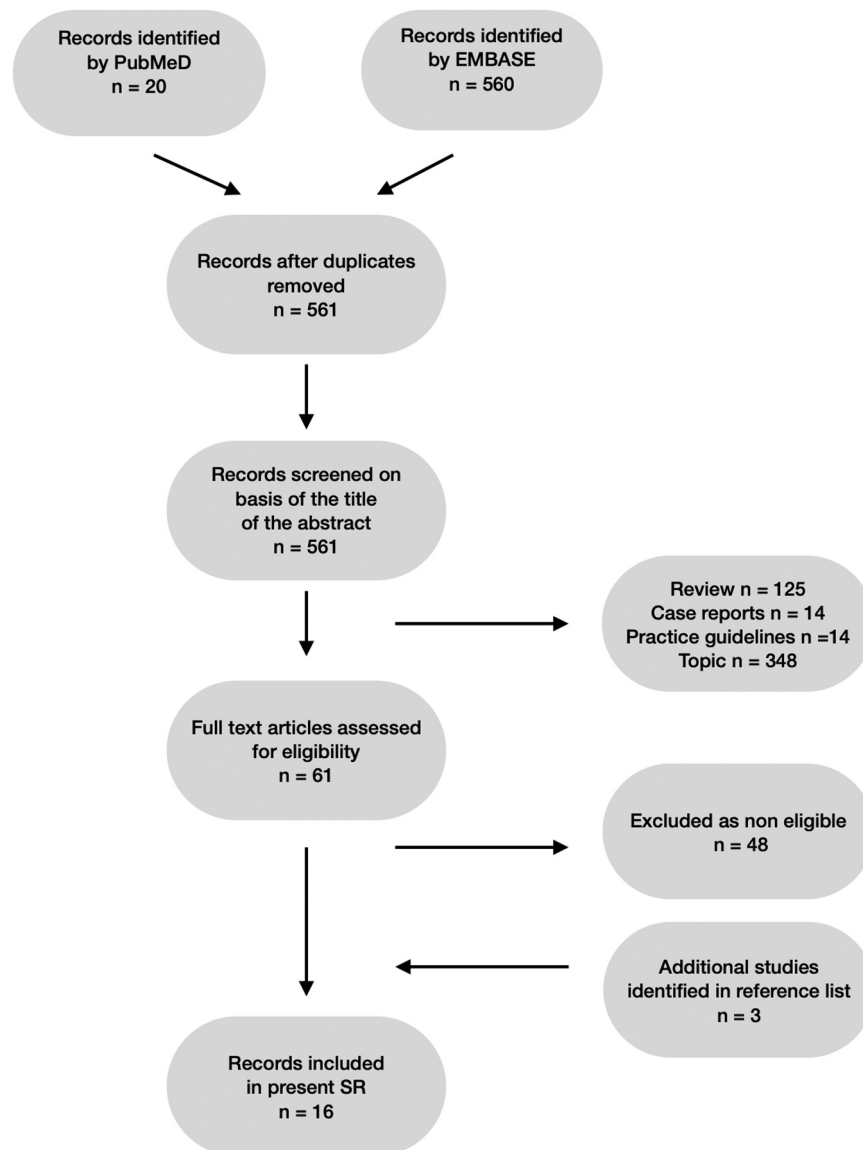


Fig. 1. Study selection for inclusion.

point-of-care clinical risk score to predict surgical site infection following open spinal fusion procedure. A SSI risk-assessment score developed by the authors used 16 predictors, including DM. The scale was stated to be a strong prediction tool for SSI risk in elective SS patients. It did not however incorporate data on preoperative HbA1c. In the light of the recommendations of The American Diabetes Association [35] as well as sound data from recent studies on patients undergoing spinal and brain surgeries [15,39] elevated HbA1c, as an important indicator of an improper glucose metabolism, should be considered a significant risk factor for postoperative infections and included in the risk stratification assessment.[40].

Majority of the studies included in present SR investigated the incidence of postoperative complications in a subgroup of DM patients.[15, 17,22–24,28–30] However, available data indicate, that elevated levels of HbA1c can be found in a group of patients with no previous diagnosis of DM.This problem was reported in a recent study on postoperative infections in a wide group of patients undergoing operative treatment. [11] Authors state, that up to 65,2% of study subjects self-reporting no diabetes were previously unaware of their metabolic derangement. This suggests that to reduce the risk of postoperative complications preoperative HbA1c testing should be considered even if no information on

glucose metabolism disorders was found in patients medical records - especially in groups of patients with high risk of glucose metabolism disorders such as obese patients. Obesity strongly correlates with the incidence of DM. Furthermore it is an independent risk factor for postoperative infections following SS procedures. [41,42] It is worth noticing, that there are data on possible lower diagnostic reliability of HbA1C in identifying dysglycemia in obese patients [43], especially of older age and larger waist circumference [44]. Despite being a recommended marker for glycemic dysfunctions HbA1C some for its characteristic may pose a challenge when used in preoperative glycemic optimization due to its lagging effect [33]. There are data confirming that in selected patients substituting parameters such as fructosamine, glycosylated albumin or 1,5-anhydroglucitol [33,45,46], may be used as surrogates for HbA1c in screening for preoperative glycemic disorders.

Reports on strategies in prevention of postoperative infections in SS commonly analyze numerous preoperative risk factors. At the same time also the outcome measures and surgery types included in the assessment are multiple.[34] Pooling all the risk factors and outcomes together blurs the picture and makes it challenging to assess the level of HbA1c above which the risk of postoperative infections increases. To recommend specific preoperative HbA1c goals the methodology of studies

should be refocused and tailored to analyze specific risk factors and outcomes in specific subgroups of surgical procedures.

There are several possible study limitations of this study. The first relates to the literature search strategy. Essential string of key words chosen to search for the research articles for this SR was short and specific. We have acknowledged the risk of having missed a part of the evidence related to investigated problem. However cross checking the reference section of selected studies enabled us to extract the majority of relevant data on investigated subject. The second one is the retrospective character of most of included research which may be associated with lower level of evidence and more potential for selection bias. To reduce this impact during the selection process we aimed for studies with a high number of patients. Included prospective studies did not prove correlation between preoperative HbA1c and postoperative infection rate. However, the overall number of patients in these studies was significantly lower comparing to the number of patients in presented retrospective protocols. We acknowledge the fact that not all included studies are equivalent. The difference in evidence value results from the diverse methodological approach. We believe, that research on a big group of subjects, with infectious complications specified as primary outcome, including exclusively SS patients can provide evidence of higher quality comparing to the research on a wider group of surgical procedures. Despite the presented limitations, considering the methodological strategy and coherence in data extraction the present SR warrants a high level of quality and accuracy to the presented data.

In conclusion the predominance of reported evidence suggest that preoperative Hb1Ac screening has substantial association with estimation of the risk to develop postoperative infections after elective spine procedures. This variable is also correlated with the risk for non-infective complications and postoperative functional outcome. There are controversies on the implementation of Hb1Ac testing as a part of routine preoperative assessment in patients scheduled for elective spine surgery. We may consider the possibility, that in patients with elevated HbA1c values the surgery may be postponed (in case of no concurrent neurologic deterioration) - to optimize the metabolic conditions and to implement specific therapeutic strategies to reduce metabolic derangement before surgery. Due to significant difference in the results of prospective and retrospective research in this area future studies should address the open controversies using an appropriate methodological design in a purposely dimensioned sample size projects.

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