Consultant360 Multidisciplinary Medical Information Network

ORIGINAL RESEARCH

PEER REVIEWED

Hemoglobin A1c Variation and Correlation With Time in Nondiabetes, Including Prediabetes

Volume 59 - Issue 12 - December 2019

Author:
Oguchi H. Nkwocha, MD, MSc
Chief Medical Officer, Clinica de Salud del Valle de Salinas, Salinas, California

Citation:
Nkwocha OH. Hemoglobin A_{1c} variation and correlation with time in nondiabetes, including prediabetes. *Consultant.* 2019;59(12):355-359.

ABSTRACT:

Objective. The purpose of the study is to determine whether hemoglobin A_{1c} in nondiabetes (which includes prediabetes) inevitably rises with time.

Research design and methods. A retrospective data review of 5742 serial A_{1c} measurements performed on 2089 patients (including patients with prediabetes) meeting the criteria of not having diabetes and having at least 2 A_{1c} measurements performed during the 33-month study period was analyzed for correlation or covariance with time. Correlation coefficient was calculated for each patient's A_{1c} series and categorized as either positive, negative, or zero. The percentages of patients with positive, negative, or zero correlation coefficients were calculated for the entire nondiabetes population and for the subset with prediabetes.

Results. A_{1c} measurements in 56% of the nondiabetes and 52% of the prediabetes subset showed positive correlation with time. Sex did not significantly affect the outcome.

Conclusions. In nondiabetes (which includes prediabetes), A_{1c} does not consistently rise with time, showing a decrease in nearly half of the patients. This finding, given the additional context of the referenced studies, supports the suggestion that absent overlaid pathophysiologic

glucose metabolic mechanisms causing diabetes, prediabetes is neither prodromal to, a precursor to, nor causal to diabetes. Programs designed to prevent diabetes by focusing on reducing A_{1c} levels in prediabetes, while successful, may be underemphasizing the real target of the interventions: underlying abnormal glucose metabolism, not prediabetes per se. Study limitations include short duration (less than 3 years) and a study population that was more than 90% Hispanic.

KEYWORDS: Diabetes mellitus, prediabetes, hemoglobin A_{1c}

Hemoglobin A_{1c} plays a significant role in the diagnosis, evaluation, and management of diabetes mellitus, as well as in the categorical diagnosis of prediabetes (defined as an A_{1c} level between 5.7% and 6.4% [39 and 46 mmol/mol], inclusive).[1] An A_{1c} level of 6.5% (48 mmol/mol) or greater is used to diagnose diabetes.[2] High A_{1c} levels predict complications in diabetes.[3] Diabetes treatment goals are currently based on A_{1c} level targets.[4]

A_{1c} values form a continuum starting from 4.1% (21 mmol/mol); under 5.7% (39 mmol/mol) is considered normoglycemia, and 5.7% to 6.4% (39 to 46 mmol/mol) is categorized as prediabetes. A_{1c} values up to 6.4% (46 mmol/mol) encompass normoglycemia and prediabetes and are considered nondiabetes; values of 6.5% (48 mmol/mol) and above are diagnosed as diabetes.

A_{1c} is also used for disease screening for diabetes and prediabetes.[5,6] The appellation *prediabetes* may compel the assumption of a natural progression from prediabetes to diabetes, as if A_{1c} relentlessly rises with time. This is reflected, for example, in the way current programs are marketed as aimed at preventing diabetes through reducing A_{1c} levels in prediabetes. One major component of these programs is education and counselling for lifestyle changes; when the latter is achieved, it has proven successful in lowering A_{1c} levels in persons with prediabetes and in decreasing progression to diabetes.[7] This result may therefore reinforce the assumption: Target prediabetes to prevent diabetes. Thus, in focusing on prediabetes as such, the program owners may have also indirectly reinforced the notion of inevitable progression to diabetes from prediabetes, at worst suggesting a causal relationship between prediabetes and diabetes.

In our clinical practice, for example, we work with patients with prediabetes; the A_{1c} levels of many of them vary up and down but generally remain in the prediabetes range or even fall below it with time, without any specific clinical intervention. If A_{1c} levels do not consistently rise with time in nondiabetes (of which prediabetes is a subset), then the noted success of programmatically preventing diabetes by decreasing A_{1c} in prediabetes must be seen within the context of some “spontaneous” decrease, regardless of intervention. In fact, Shang and

colleagues, in their 12-year population cohort study, concluded that among older adults, approximately 19% with prediabetes may revert to normoglycemia, and only 11% progress to type 2 diabetes.[8]

Research findings such as this still do not answer the question: How does A_{1c} generally behave in relation to passing time in nondiabetes (defined as no diagnosis of any type of diabetes, which includes prediabetes)? Does it consistently rise with passing time, implying inevitable progression to diabetes, or does it decrease with increasing time?

We set out to explore this question by retrospectively analyzing serial A_{1c} measurements performed on nondiabetic patients to determine whether there is universal positive covariance of A_{1c} levels with time (that is, an increase in A_{1c} as time increases), which would suggest progression with time, during the 33-month study period between 2015 and 2018.

METHODS

Study type. Retrospective record review of patient's A_{1c} blood test results data from a multispecialty primary care health care provider organization from October 2015 through June 2018 (33 months).

Institutional review board (IRB) clearance. The study was determined by the IRB of the Clinica de Salud del Valle de Salinas, Salinas, California, as not requiring IRB review.

Data source and repository. Laboratory (Foundation Laboratory, Pomona, California).

Data access. Authorized programmatic data read-in from the laboratory secure FTP subfolder.

Data management and analysis. R programming language was used throughout.

Protection of identifiable patient information. Accomplished by relevant data field "one-way" anonymization (meaning that de-anonymization or re-identification of the patient was not possible), using the Anonymizer R package function.

Data structure. Original data fields included test type, diagnosis, date of resulting, age, sex, and results; rows were laboratory test transactions for individual patients by dates and diagnosis.

Inclusions. Only records where A_{1c} or mean plasma glucose (MPG) was measured—in some of the records, only the latter was reported; where this was the case, MPG results were converted to A_{1c} using the standard conversion formula, $MPG = (35.6 \cdot A_{1c}) - 77.3$.

Exclusions. All records with a diagnosis of any type of diabetes using the following ICD-9 (International Classification of Diseases, Ninth Revision) and ICD-10 (International Classification of Diseases, Tenth Revision) codes: type 1 diabetes mellitus, 250.xx or E10.xx;

type 2 diabetes mellitus, 250.xx or E11.xx; and gestational diabetes (diabetes mellitus in pregnancy, childbirth, and the puerperium), 648.83 or O24.xx.

Categorical diabetes was defined as $A_{1c} \geq 6.5$ (48 mmol/mol).

The following Boolean statement (in R programming language) was used to accomplish the subsetting:

!(Dx >= "E0"& Dx <"E14" | Dx>="250" & Dx <"251"| Dx=="648.83"| Dx >="O24" & Dx <"O25" |Result >=6.5)

The resulting data subset represented all patient records without the diagnosis of any type of diabetes; each unique patient had a series of A_{1c} measurements over the study period. The subgroup with a diagnosis of prediabetes based on A_{1c} range of 5.7% to 6.4% (39 to 48 mmol/mol) was identified. Subgrouping by sex was also done, but not by age, since the age varied for the same patient during the 3-year study period.

Statistical method. To determine whether serial A_{1c} levels (performed usually at least 3 months apart) increased or decreased with time, the method used involved calculating the correlation coefficient of the change of A_{1c} with change in time for each patient, categorizing the resulting coefficient as zero (no correlation), less than zero (negative; ie, A_{1c} decreasing as time increased), or positive (ie, A_{1c} increasing with time). The correlation coefficient method is appropriate for the research question, because it determines covariance between 2 independent numeric variables (A_{1c} and time) that are both changing. The magnitude of the correlation was not important to the study, only the sign: negative, neutral (zero), or positive. Since at least 2 serial A_{1c} values are required in order to calculate a correlation coefficient, records with only one A_{1c} measurement performed during the study period were excluded. Calculations of the correlation coefficient were performed on each remaining record using the standard Pearson method for correlation coefficient determination with the R function cor(). Time, originally represented in the data as calendar dates, was first converted to numeric dates format for the calculations.

Plots and tables. Examples of individual records (3 in all, representing positive, negative, and zero coefficients) subjected to correlation coefficient determination were plotted. The frequencies of the resulting coefficients were plotted as a histogram for visual analysis for the main population and then for the prediabetes subgroup. A table was constructed showing the number of A_{1c} values in the series of each record (2 to 17) and how many records had that number in the series. A second table showed the percentage of patients (records) in each group whose A_{1c} series had zero, positive, or negative correlation coefficient values.

RESULTS

Laboratory Tests

All test results in original database: 2,944,236.

A_{1c}-only test results: 73,508; range, 4.1% to 20% (21 to >151 mmol/mol).

A_{1c} test results after the exclusion of diabetes: 39,465; range, 4.1% to 6.4% (21 to 46 mmol/mol).

Patients

Unique patients—diabetic patients excluded: 11,907. Sex distribution: 7261 females (61%); 4645 males (39%), and 1 unknown sex. Age range: 3 to 98 years.

Groups

Nondiabetes (NoDM): n = 11,907; females, 61%; males, 39%; A_{1c} <6.4% (46 mmol/mol).

Prediabetes (PreDM): n = 10,631; females, 60%; males, 40%; A_{1c} 5.7 to 6.4 (39 to 46 mmol/mol).

Records

Serial A_{1c} values with at least 2 measurements: NoDM = 5742 patients; PreDM = 5644 patients. Unique records with A_{1c} values (at least 2 A_{1c} measurements in series): NoDM = 2089 records; PreDM = 2089 records.

Table 1 shows the count of A_{1c} measurements in each series and how many records (sorted by the latter), along with percentages, had that count. The range of A_{1c} counts was 2 to 17 in a series.

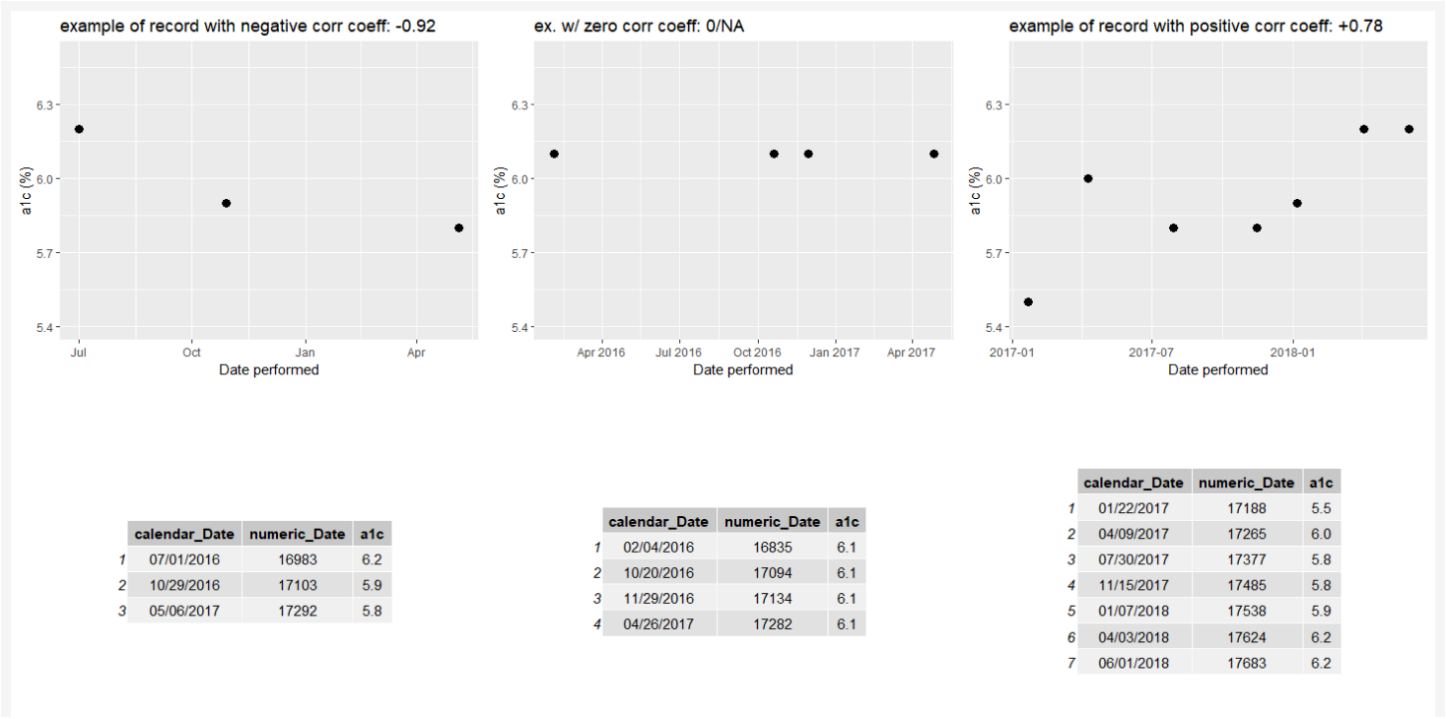
a1c.count.in.series	nbr.records	percent.records	Cum..Percent.records
2	1244	59.6	59.6
3	484	23.2	82.7
4	187	9.0	91.7
5	92	4.4	96.1
6	42	2.0	98.1
7	16	0.8	98.9
9	9	0.4	99.3
8	6	0.3	99.6
17	2	0.1	99.7
12	2	0.1	99.8
10	2	0.1	99.9
16	1	0.0	99.9
15	1	0.0	100.0
13	1	0.0	100.0
Total	2089	100.0	100.0

Table 1. *Distribution of records by count of A_{1c} in series.*

This table shows the count of A_{1c} measurements in each record-series and how many records (with percentages) have that count. Range of A_{1c}-count in series is 2 to 17. Most of the records (98%) had 6 or fewer A_{1c} measurements over the study period. The table is sorted by number of records (nbr.records). This table is for NoDM; the PreDM data are similar: most of the records fall into less than 6 A_{1c} values in the series.

Correlation Coefficients

Figure 1 shows 3 records, each with serial A_{1c} measurements, examples of individual records where the correlation coefficient is negative, zero, or positive, respectively. It is a combination figure with plots and tables displaying the same data.



	calendar_Date	numeric_Date	a1c
1	07/01/2016	16983	6.2
2	10/29/2016	17103	5.9
3	05/06/2017	17292	5.8

	calendar_Date	numeric_Date	a1c
1	02/04/2016	16835	6.1
2	10/20/2016	17094	6.1
3	11/29/2016	17134	6.1
4	04/26/2017	17282	6.1

	calendar_Date	numeric_Date	a1c
1	01/22/2017	17188	5.5
2	04/09/2017	17265	6.0
3	07/30/2017	17377	5.8
4	11/15/2017	17485	5.8
5	01/07/2018	17538	5.9
6	04/03/2018	17624	6.2
7	06/01/2018	17683	6.2

Figure 1. *Example records with serial A_{1c} measurements showing negative, zero, and positive correlation coefficients.*

Three records each showing serial A_{1c} values on a time-axis rendered in calendar dates in the plots and also in numerical date format in the associated table in the bottom column. The left panel is an example of a negative A_{1c}-time correlation coefficient (-0.92); the right panel is positive (+0.78). The middle panel shows an A_{1c} value that is unchanged with time; functionally, this is read as zero correlation coefficient, although the calculated value is "not applicable (NA)," because zero appears as one of the terms. In the NoDM group, there 593 records with negative coefficients, 334 with zero, and 1162 with positive coefficients.

Figure 2 depicts the histograms of all the 2089 coefficients calculated for each record of each of NoDM and PreDM groups, respectively. Range for NoDM: -1 to +1; and for PreDM: -1 to +1.

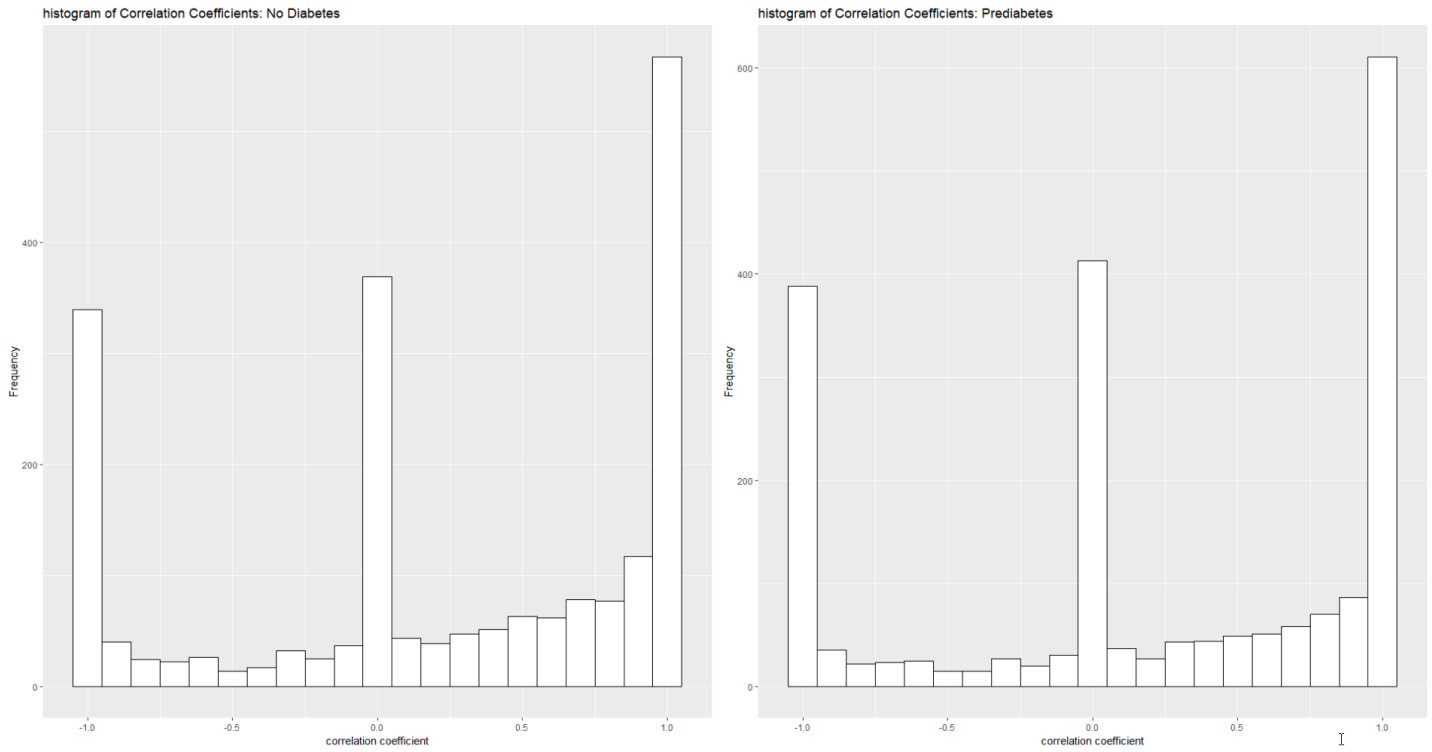


Figure 2. *Histograms of A_{1c}–time correlation coefficient computations.*

The plot shows the histograms of all the 2089 correlation coefficients calculated for each record of each of NoDM and PreDM groups. The range is -1 to +1.

Distribution of Positive, Negative, and Zero Coefficients

Table 2 is a tabular presentation of the counts of negative, zero, and positive coefficients for both NoDM and PreDM groups, respectively, and their percentages.

NoDM (n = 2089): 56% positive; 28% negative; 16% zero.

PreDM (n = 2089): 52% positive; 29% negative; 18% zero.

Grp	nbr_neg	nbr_zero	nbr_pos	Total	prcnt_neg	prcnt_zero	prcnt_pos
Prediabetes	611	384	1094	2089	29	18	52
No Diabetes	593	334	1162	2089	28	16	56

Table 2. *Distribution of records by negative, zero, and positive A_{1c}–time correlation coefficient.*

Tabular presentation of the counts of records with negative, zero, and positive coefficients for both NoDM and PreDM groups, and their percentages. In all, 52% of PreDM records showed a positive A_{1c}–time correlation coefficient, while 56% of the NoDM group showed positive coefficients.

Sex

The sex of the patients did not meaningfully affect the outcome; thus, the analysis is not included.

Results Summary

Slightly more than half of the patients who had serial A_{1c} measurements performed during the study period (n = 2089) showed a rising pattern (positive correlation coefficient with time) in their A_{1c} levels, while the rest showed either a decline or zero pattern (negative or no correlation with increasing time), in both the NoDM group and the PreDM subset. Sex had little if any effect on the outcome.

CONCLUSIONS

In patients without diabetes, serial A_{1c} levels do not invariably rise with time; only slightly more than half of the cases showed a positive correlation with increasing time in this study; gender did not affect the results. This A_{1c}-time relationship was determined by the use of Pearson correlation statistical method. The study itself is limited by a duration of less than 3 years (33 months) and a relatively nondiverse population (approximately 90% Hispanic); age (range 3 to 98 years) did not significantly affect the outcome and was not part of the final analysis.

The same conclusion applies to patients with prediabetes, a subset of patients without diabetes: A_{1c} levels do not inexorably rise with time. The wider implication is that prediabetes (based on A_{1c} categorization) does not as a rule develop into diabetes with time; that is, prediabetes is not necessarily a precursor to diabetes. It takes the presence of abnormal glucose metabolism resulting in uncontrolled hyperglycemia to get to diabetes. Without the superimposition of this pathophysiology on a nondiabetic or prediabetic population, A_{1c} progression to diabetes is probably unlikely. As Shang and colleagues found in their study, for example, only 11% of patients with prediabetes progressed to diabetes, while more (19%) reverted to normoglycemia.[8] An interpretation is that those prediabetic individuals progressing to diabetes in all likelihood met the condition of existent significant glucose metabolic pathophysiology, which is what led to diabetes.

Finally, while A_{1c} forms a numerical continuum from normoglycemia to hyperglycemia through prediabetes to diabetes, the implications of A_{1c} values in nondiabetes are different from those in diabetes. For example, Yong and colleagues[9] concluded that “prediabetes as defined by HbA_{1c} levels is not a risk factor for adverse outcomes after surgery,” while Sherwani and colleagues[1] found that elevated A_{1c} has also been regarded as an independent risk factor for coronary heart disease and stroke in persons with or without diabetes. Elsewhere, Paprott and colleagues[10] reported that “HbA_{1c} levels in the prediabetic range were not associated with an increased

mortality risk."

Diabetes is definitely more than an A_{1c} disease and probably other than an A_{1c} disease. When determining the need for and efficacy of interventions aimed at reducing A_{1c} levels in nondiabetic persons (including prediabetic individuals) for the purpose of preventing or delaying diabetes, investigators may want to emphasize that the real target of the interventions is the underlying pathophysiologic glycemic mechanisms, not A_{1c} per se or prediabetes. Otherwise, the risk of unintentionally promoting the concept of prediabetes as a prodrome of diabetes, thereby inviting the assignment of causation, remains high, as is the risk that health insurance companies may decide to categorize prediabetes as a preexisting illness with respect to diabetes.

Prediabetes, a categorical diagnosis, has not been shown to evolve into diabetes, to our knowledge. Programs directed at prediabetes,[11] which succeed in reducing A_{1c} in that group, and or in preventing diabetes, are effective only to the extent that they have a favorable impact on the abnormalities of glucose metabolism when such are already present in the individual.

References

1. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. *Biomark Insights.* 2016;11:95-104.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2014;37(suppl 1):S81-S90.
3. Laiteerapong N, Karter AJ, Moffet HH, et al. Ten-year hemoglobin A1c trajectories and outcomes in type 2 diabetes mellitus: the Diabetes & Aging Study. *J Diabetes Complications.* 2017;31(1):94-100.
4. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2018. Diabetes Care.* 2018;41(suppl 1):S55-S6
5. The A1C test & diabetes. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis/a1c-test. Published April 2018. Accessed June 19, 2019.
6. Pippitt K, Li M, Gurgle HE. Diabetes mellitus: screening and diagnosis. *Am Fam Physician.* 2016;93(2):103-109.
7. Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes Care.* 2002;25(12):2165-2171.
8. Shang Y, Fratiglioni L, Marsegilia A, et al. Incidence and evolution of prediabetes among older adults—a population-based cohort study. *Diabetes.* 2018;67(suppl 1):LB49. doi:10.2337/db18-177-LB.
9. Yong PH, Weinberg L, Torkamani N, et al. The presence of diabetes and higher HbA_{1c} are independently associated with adverse outcomes after surgery. *Diabetes Care.* 2018;41(6):1172-117
10. Paprott R, Schaffrath Rosario A, Busch MA, et al. Association between hemoglobin A_{1c} and all-cause mortality: results of the mortality follow-up of the German National Health Interview and Examination Survey 1998. *Diabetes Care.* 2015;38(2):249-256.

11. Shubrook JH, Chen W, Lim A. Evidence for the prevention of type 2 diabetes mellitus. *J Am Osteopath Assoc.* 2018;118(11):730-737.