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# Variations in glucose/C-peptide ratio in patients with type 2 diabetes associated with renal function

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## ABSTRACT

**Introduction:** Accurate dosing of medications for glycemic control is a challenge for clinicians in diabetic patients with kidney disease. Diminishing glomerular filtration rates are associated with decreased renal clearance of insulin and increased prevalence of hypoglycemic episodes. Measurement of glucose/C peptide ratios may be useful to guide dosing in those patients who receive powerful insulin secretagogues as glomerular function decreases with age and disease.

**Methods:** In order to determine the relationship between glucose, C-peptide and renal function, we reviewed the records of patients with type 2 diabetes followed in our kidney hypertension clinic who met the following criteria: age 35–90 years, requirement of medications to control glycemia, at least 4 simultaneous measurements of C peptide, HbA1c, creatinine and blood glucose.

**Results:** 87 patients (67 males, 20 females), ages  $67.1 \pm 10.6$  years, BMI  $32.5 \pm 5.2$ , A1c  $8.2 \pm 1.2\%$ , eGFR  $73 \pm 27.2$  ml/min, had glucose/C-peptide ratios  $60.7 \pm 46.4$ . 59% of the total group were taking insulin secretagogues. Patients were divided into groups based upon mean eGFR and use or absence of insulin secretagogues. Glucose C-peptide ratios were lowest in the quartile of patients with the lowest eGFR (<50 ml/min).

**Conclusion:** Diminished renal function and advanced age are associated with the lowest glucose/C-peptide ratios, independent of achieved glycemic control. With similar use of secretagogues, glucose/C-peptide ratio were lower when eGFR was  $\leq 49$  ml/min compared to  $>50$ –80 ml/min. Use of secretagogues was associated with decreased glucose/C-peptide levels. In patients with reduced renal function (eGFR < 50 ml/min), use of insulin secretagogues may be associated with lower glucose/C-peptide ratios associated with higher risks for hypoglycemic reactions.

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## 1. Introduction

Clinicians and patients may find it increasingly challenging to manage blood glucose levels and avoid hypoglycemia in diabetes mellitus as renal function declines. This is likely related

to the established physiology of insulin [1] and C-peptide [2] in renal tubular metabolism/excretion. Although we can anticipate a loss of 1–2 ml/min/year in estimated glomerular filtration rate (eGFR), many patients with Type 2 diabetes mellitus (T2D), hypertension and microalbuminuria do not

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demonstrate a need for substantial changes in medication dosages over long periods of time. However, a minority of patients may experience more rapid declines in eGFR leading to increased risks of hypoglycemia when glucose modifying medications are renewed without dose titration.

Over the past 20 years in the United Kingdom, a portion of the data base research for the National Health Service has been devoted to the Clinical Practice Datalink, which includes 240,000+ patients with T2D. During this period of follow-up, the observed incidence of hospitalizations for hypoglycemia has tripled for patients 65–79 years of age [3]. This is a period in which eGFR may theoretically have declined from >60 to <45 ml/min.

Capillary and continuous blood glucose monitoring permits patients with diabetes to make immediate adjustments to their diet or dose of anti-hyperglycemic agents. Meanwhile fructose-amine or glycohemoglobin A1c provide insight into the average blood glucose for the prior 30–90 days. For a proactive patient with knowledge of how to use these devices and keen cognitive awareness to interpret their glucose data, there may be no need for another marker of glycemia control. However, as pancreatic and renal function as well as insulin sensitivity change over years of follow-up, there are instances wherein another warning system may be helpful. In this manner, investigators from the University of Exeter Medical School [4] have identified a sub-group of patients with T2D at risk for developing hypoglycemia through the use of a random C-Peptide assay: individuals with lower levels of C-Peptide secretion, receiving insulin injections, were subject to twice as many episodes of hypoglycemia which lasted three times as long as patients who had more robust random C-peptide levels as assessed by continuous glucose monitoring. Since study subjects were 70 years old or greater and had eGFR levels >30 ml/min; this raises the possibility that the risk of hypoglycemia increases with diminishing metabolism/excretion of insulin as eGFR falls below 50 ml/min.

We have previously reported cases of hypoglycemia associated with acute [5] or chronic [6] kidney failure in patients with T2D. Hypoglycemia developed rather abruptly following coronary angiography in screening for kidney transplantation [7] and this prompted us to identify individuals at risk of developing hypoglycemia at an earlier stage in their disease progression [8]. Finally, this culminated in a trial of saline infusion as protection prior to angiography [9]. We hypothesized that the increased risk of hypoglycemia was associated with decreased metabolism/excretion of insulin as renal function declined. To test this hypothesis in patients with T2D, we have documented blood glucose and C-Peptide (insulin assay) levels simultaneously at different stages of chronic kidney disease in seen in our Kidney/Hypertension Clinic.

## 2. Patients and Methods

We reviewed charts for all patients seen by select providers in the Kidney/Hypertension Clinic at the Joslin Diabetes Center and selected those who met the following inclusion criteria:

Aged between 40 and 90 years AND diagnosed with Type 2 diabetes requiring medications for hyperglycemia AND who had at least 4 simultaneous measurements of C peptide,

HbA1c, creatinine and blood glucose. For those patients that were eligible for participation, age, gender, BMI, diabetes medications and ranges of all measurements were abstracted from their records.

Medical records of patients with T2D seen in the Kidney/Hypertension Clinic in 2017 were reviewed. Control patients with normal kidney function were identified based on a sustained a sustained estimated glomerular filtration rate (eGFR) greater than 60 ml/min. while Individuals in the observation group were had eGFRs less than 60 ml/min. Other inclusion criteria included at least 4 visits with simultaneous measurements of glucose and C-Peptide over multiple years up for control subjects but only a single visit with these simultaneous measurements in the observational group.

Exclusion criteria included unstable liver function, defined as greater than twice the upper limit of normal for liver enzymes. Patients were not excluded solely on the basis of hepatic steatosis or prior intolerance of protein intake which was subsequently resolved or for liver transplantation with a normal functioning allograft. Study subject with normal functioning kidney allograft were not excluded.

A subgroup of subjects who were prescribed more powerful insulin secretagogues, such as sulfonylureas (glipizide, glimepiride, glyburide) or glinides (repaglinide, metaglinide). The secretagogue subgroup did not include subjects prescribed glucose-dependent insulin secretagogues such as glucagon-like agonists (exenatide, liraglutide, dulaglutide) or dipeptidyl peptidase 4 (dpp4) inhibitors (sitagliptin, linagliptin).

All information is summarized using means and standard deviations or for skewed variables, medians and interquartile ranges for continuous variables and using counts and percentages for dichotomous variables. Global tests of equality are conducted using ANOVA, the Kruskal-Wallis test and Pearson's chi-squared test, respectively. P-values less than 0.05 are considered significant.

C peptide was performed by the commercially available Elecsys method (Cobas, Modular Analytics E170, Roche Diagnostics, Indianapolis, Indiana) using a monoclonal C-peptide specific antibody plus a monoclonal C peptide specific antibody labelled with a ruthenium complex to form a sandwich complex, which becomes bound in a solid phase. Chemiluminescent emission was measured by a photomultiplier. Glucose/C-Peptide ratios are reported in units (mg/dl/ng/ml).

## 3. Demographics

87 patients met the age, type 2 diabetes, and measurement requirements for involvement in this study and their demographics are described in Table 1. This group was comprised of 67 males and 20 females aged  $67.1 \pm 10.6$  years, with BMI of  $32.5 \text{ kg/M}^2$ , A1c of 8.21.2% and mean eGFR of  $73 \pm 27.2$  ml/min. Of these patients 59% had been prescribed insulin secretagogues. For purposes of analysis of this cohort of patients renal function was considered only mildly reduced if EGFR was  $\geq 60$  ml/min. 56 patients had only mildly reduced renal function (31 met criteria for more advanced renal dysfunction). Our analysis was designed to assign patients to groups based upon use or non-use of insulin secretagogues, as well as level of renal function ( $\geq 60$  ml/min vs. <60 ml/min, quar-

**Table 1 – Demographics.**

Patient groups	n	Gender	Age	BMI	HbA1c	eGFR
Total	87	67m/20f	67.1 ± 10.6	32.5 ± 5.2	8.2 ± 1.2	73 ± 27.2
Secretagogues + eGFR ≥ 60	51	41/10	67.3 ± 10.7	31.7 ± 4.7	8.2 ± 1.6	75.7 ± 25.7
eGFR < 60	35	27/8	66.2	31.6	8.9	91
Secretagogues – eGFR ≥ 60	36	26/10	66.8 ± 10.5	33.4 ± 5.7	8.1 ± 1.2	69 ± 7.8
eGFR < 60	21	15/6	62	34.6	8.1	90
	15	11/4				

tiles of renal function) in order to determine whether there was an interaction between C-peptide level of degree of renal function. No statistically significant or clinically meaningful gender differences were noted between any of the subgroups.

#### 4. Results

Table 2a lists results (eGFR, glucose/C-Peptide) for T2D study subjects in the control group (eGFR > 60 ml/min). Table 1a lists individuals who had received powerful secretagogues and Table 1b list individuals who had not received powerful insulin secretagogues. Table 2b lists results (eGFR, glucose / C-Peptide) for T2D patients with eGFR < 60 ml/min some of whom would have received powerful insulin secretagogues at some point in their follow-up + some who would not have received powerful insulin secretagogues at any point in their follow-up. Table 3 details the Impact of the use of sulfonylureas and other secretagogues on glucose C-peptide relationships grouped as well by levels of renal function. Fig. 1 demonstrates changes in changes in renal function and glucose/C-peptide levels in a single patient during several years of follow up.

#### 5. Discussion

The current study found on average a glucose/C-Peptide ratio of 65 for the study group with normal kidney function (eGFR > 60 ml/min). For the study group with eGFR < 60 ml/min, the glucose/C-Peptide ratio was on average 45 mg/dl/ng/ml. Within the normal kidney function group, there was a modest difference in glucose/C-Peptide ratio between the subgroup on no sulfonylurea medication (74 units) vs the subgroup on sulfonylurea medications (59 units). But for the study group with eGFR < 60 ml/min, there was no difference between the subgroup not receiving sulfonylurea drugs (45 mg/dl/ng/ml) vs the subgroup receiving sulfonylurea drugs (45 units). From observations in Tables 1 and 2 it can be concluded that increases in C-peptide secretion secondary to secretagogues or decreases in C-peptide excretion due to renal insufficiency have profound effects on glucose C-peptide ratio. Compared to diabetic patients with eGFR > 90 ml/min, the study group with eGFR < 30 ml/min demonstrated progressive lowering of glucose/insulin ratio, associated at some point with recording of clinically significant lower blood glucose concentrations. Therefore, doses of anti-hyperglycemic medications had to be decreased, predominantly when eGFR had fallen to less than 45 ml/min.

When the study participants were analyzed in quartiles based on eGFR, it was possible to confirm in quartiles 1 and 2 that glucose C-peptide ratios are significantly lower (45 vs 75) at levels below 40 ml/min [10] due to impaired metabolic clearance.

In the current series, five study subjects with persistent loss of kidney function were able to discontinue insulin therapy while one subject's insulin requirement decreased to a low dose. In addition, two study subjects were able to discontinue insulin secretagogues while five others were able to decrease to low-dose, thus glucose lowering therapy was reduced in 11 subjects. In this medical center, there has been a trend away from multiple-doses of insulin and insulin secretagogues in favor of simplified programs for geriatric patients who are at risk for confusion and falling [11] In two important reports, ketosis-prone study subjects with T2D and preserved Beta cell function, 7 of 62 (11%) [12] and 9 of 83 (11%) patients were able to discontinue insulin and oral agents after 12 months of diet/exercise treatment [13]. Unfortunately, kidney function was not included in these two publications as shown in our Fig. 1.

Prior studies of hypoglycemia associated with loss of eGFR have mainly involved Type 1 diabetic patients although dosage adjustment with acute or chronic kidney function has at times been a subject of interest. The current report concentrates on patients with T2D, virtually all of whom are under treatment with diuretics and anti-hypertensives anti-angiotensin agents once microalbuminuria is detected even at normal estimated glomerular filtration rate. Newer classes of anti-hyperglycemic medications which are glucose-dependent insulin secretagogues have not been analyzed separately in this study. However, if glucagon-like peptide agonists or sodium-glucose transport inhibitors manage to decrease blood glucose while inducing dehydration through gastric or renal tubular losses, then glucose/insulin ratios will fall and there will be a risk of hypoglycemia if doses of anti-hyperglycemia drugs are not decreased.

From the Action to Control Cardiovascular Complications of Diabetes (ACCORD) study, it was learned among 10,000+ study subjects with T2D, aged 40–80 years, random assignment to standard glycemia control to a glycohemoglobin A1C of 7.1% vs assignment to intensive glycemia control down to A1C 5.9%, resulted in a statistically superior outcome for the sub-group who achieved an A1C of 7.4% vs 6.4% for the intensive sub-group at 3.5 years [14]. In a subsequent analysis, the ACCORD investigators in conjunction with Collaborators on Trials of Lowering Glucose (CONTROL) group sought to

**Table 2a – Quartiles of estimated Glomerular Filtration Rate (eGFR).**

EGFR groups	eGFR mean	Age (years)	A1c	BMI	Glu/Cpep	Meglitinide	Sulfonylurea	Secretagogues
1 (n = 23)	34.87 ± 13.82	69.65 ± 12.74	7.87 ± 1.49	32.14 ± 5.74	44.22 ± 24.70	3	9	12
2 (22)	69.86 ± 8.19	70.68 ± 8.48	8.02 ± 1.08	33.09 ± 5.37	75.00 ± 69.31	1	10	11
3 (21)	87.71 ± 3.80	67.71 ± 7.78	8.54 ± 0.99	31.84 ± 5.91	71.43 ± 48.79	1	13	14
4 (21)	103.10 ± 5.66	59.90 ± 9.40	8.19 ± 0.94	32.48 ± 3.49	52.90 ± 21.36	0	14	14
p	0.001	0.002	0.26	0.88	0.08	0.30	0.21	0.53

clarify why many patients with T2D treated intensively to an A1C of 6.5% have done so very well, particularly in the area of microvascular complications [15]. The answer in a recent publication [16] appears to be that for individuals considered to be at high mortality risk in terms of a composite score, the impact of hypoglycemia risk appears to be intolerable. On the other hand, among patients with T2D with low mortality risk, an intensive glycemia program was acceptable. While there was no emphasis on renal function in the composite score presented in the recent ACCORD study report [16] renal function was the specific subject of interest from the prospective study of 14,000+ study subjects in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study [17]. The TECOS study group found severe hypoglycemic events to occur nearly twice as frequently for their sub-group with eGFR < 60 ml/min (37%) vs 22% in the sub-group with eGFR > 60 ml/min. The TECOS investigators were able to confirm the observations of the ACCORD team in identifying an at-risk T2D frail patient phenotype. This at-risk sub-group was older within the range of 50–80 years and had a lower eGFR: 64 (52–83) vs. 73 (60–88) ml/min than the lower risk cohort.

Investigators from the University of Utah and Washington University demonstrated the mechanism of death from insulin-induced hypoglycemia in the streptozotocin diabetic rat to be associated with second and third-degree heart block [18], consistent with high-risk associations of both ventricular ectopy and atrioventricular delay on ambulatory EKG in diabetic patients on chronic dialysis [19]. A recent study from multiple dialysis centers in France using implantable loop recorders [20] has identified an association of hyperkalemia with conduction disorders vs. hypokalemia with ventricular arrhythmia. Since the patient completing a dialysis treatment is likely to be at both a lower serum potassium due to use of bicarbonate dialysate and lower blood glucose due to removal of uremic toxins that cause insulin resistance [21], there is a risk for ventricular arrhythmia on the way to work or back home. Of the 71 dialysis patients studied, 42 (59%) were listed

in the diabetes sub-group, which accounted for all of the individuals who suffered a sudden death. Arrhythmia-risk with hypoglycemia in type 1 diabetic patients has been recorded on ambulatory EKG as bradycardia overnight with tachycardia when hypoglycemia occurred during the day [22]. While there has been some debate concerning a distinct time distribution for brady- vs tachycardia, what has not been questioned is the association of hypoglycemia with atrial ectopy, disturbances in atrioventricular conduction, variations in QT interval, and ventricular ectopy. [23]. Patients with T2D on glipizide with a lower eGFR were more likely to record ventricular ectopy with ambulatory EKG than patients with T2D on glyburide with a higher eGFR [24].

In this connection, diabetic cardiomyopathy [25–27] with intermittent crises of hypoglycemia from insulin injections and takotsubo cardiomyopathy [28,29] with intermittent crises of hypertension from pheochromocytoma both demonstrate the risks of repeated catecholamine stimulation, i.e., electrophysiological abnormalities with inefficient ventricular contraction in the absence of coronary artery obstruction.

Another consideration of the frail patient was achieved through analysis of data from the EXAMINE trial of the dipeptidyl peptidase 4 inhibitor, alogliptin, involving a 1.5-year follow-up of patients with T2D who had recently survived an acute coronary event [30]. Of the 5367 study subjects, 5269 (98%) were considered to have stable kidney function while 98 (2%) were found to have unstable kidney function. Of those 98 subjects with unstable kidney function, 30 (0.7%) had a 50% decline in eGFR without reaching 15 ml/min vs 68 (1.3%) who had fallen to 15 ml/min or lower (Stage 5 kidney failure). In the current smaller report, 25 (29%) of study subjects had a fall in eGFR to <45 ml/min and 10 (12%) individuals recorded levels <30 ml/min.

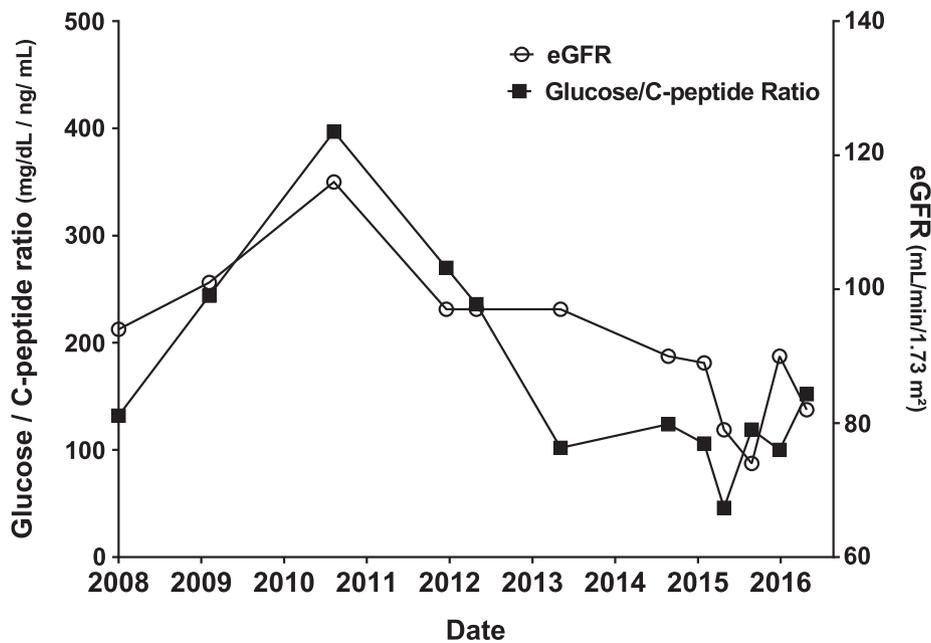
A study of hypoglycemia risk during recovery from acute kidney injury in-hospital was conducted using records from the Veterans Health Administration [31]. From a type 2 diabetes study group of 65,000+ participants, 45% appeared to have complete recovery, 41% had partial recovery, and 14%

**Table 2b – Quartiles of glucose/C-peptide ratio.**

Glucose/C-peptide groups	eGFR mean	Age (years)	A1c	BMI	Glu/Cpep	Meglitinide	Sulfonylurea	secretagogues
1 (n = 22)	59.59 ± 35.19	68.73 ± 10.36	7.30 ± 1.26	32.16 ± 5.38	25.86 ± 6.43	1	15	16
2 (23)	73.13 ± 23.86	65.48 ± 13.33	8.00 ± 0.91	31.87 ± 3.84	41.96 ± 4.91	2	10	12
3 (21)	83.14 ± 20.26	65.19 ± 8.69	8.51 ± 0.75	31.19 ± 5.02	59.19 ± 6.50	1	13	14
4 (21)	76.52 ± 23.07	69.05 ± 9.06	8.84 ± 1.11	34.39 ± 6.04	119.10 ± 61.97	1	8	9
p	0.032	0.49	0.001	0.21	0.001	0.92	0.14	0.18

**Table 3 – Impact of the use of sulfonylureas and other secretagogues on glucose C-peptide relationships.**

	Sulfonylurea Negative (n = 41)	Sulfonylurea Positive (n = 46)	P value	Secretagogue Negative (n = 36)	Secretagogue Positive (n = 51)	P value
Age	67.88 ± 10.92	66.39 ± 10.29	0.52	66.75 ± 10.52	67.33 ± 10.68	0.80
A1c	8.05 ± 1.15	8.24 ± 1.18	0.44	8.09 ± 1.18	8.19 ± 1.16	0.71
BMI	33.03 ± 1.15	31.83 ± 4.67	0.29	33.35 ± 5.69	31.73 ± 4.70	0.15
eGFR mean	66.73 ± 28.02	78.48 ± 25.55	0.044	69.03 ± 27.82	75.71 ± 26.73	0.26
Glucose/C peptide ratio	68.78 ± 56.47	53.43 ± 34.25	0.12	70.75 ± 58.85	53.55 ± 34.06	0.09
Meglitinides	5 (12.2%)	0	0.015	0	5 (9.8%)	0.05
eGFR quartiles						
≤49 ml/min	14 (34.1%)	9 (19.6)	0.21	11 (30.6%)	12 (23.5%)	0.53
>50 to ≤80	12 (29.3)	10 (21.7)		11 (30.6)	11 (21.6)	
>80 to ≤95	8 (19.5)	13 (28.3)		7 (19.4)	14 (27.5)	
>95 to 114	7 (17.1)	14 (30.4)		7 (19.4)	14 (27.5)	

**Fig. 1 – Longitudinal follow up of a single patient for illustration.**

had no recovery from in-hospital acquired acute kidney injury. Outpatient follow-up determined 1% of glucose data had been gathered at re-admission to hospital for hypoglycemia, 13% at revisit to Emergency Department for hypoglycemia, and 86% from outpatient determination of a glucose <60 mg/dl within 90 days from hospital discharge. Investigators from Vanderbilt University determined the matched group without an episode of hospital-acquired acute kidney injury had a 27% lower risk for hypoglycemia. Post-hospitalization, individuals with no recovery from acute kidney injury had a hazard ratio (HR) of 1.5/1.0 (1.4–1.6) for subsequent episodes of hypoglycemia with an HR of 1.27 (1.2–1.3) for hypoglycemia with partial recovery vs. complete recovery from acute kidney injury. A quote from this publication appears to be entirely appropriate for our small study: “The risk of hypoglycemia in these patients may increase owing to variability in timing and amount of nutrient increase, acute illness itself, a lack of counter-regulatory

mechanisms, and further decrements in kidney function that may not be appreciated”. Fig. 1 from our experience exemplifies the general trend of falling glucose/C-peptide ratio as eGFR diminishes with aging. But as pointed out by the Vanderbilt investigators there are unexplained short-term deviations from the curve which may be difficult to explain.

## 6. Limitations

General experience with glucose/C-peptide testing is rather limited despite the fact that such testing is simple and relatively inexpensive. This is a small, single center retrospective series from a tertiary referral center. Further studies would be needed to establish the generalizability of these results. The glucose/C-peptide ratios, and renal functions used in our calculations were the mean results for each individual over a period of years. As such, they do not represent a single point in time and cannot be compared with such measurements.

These observations would therefore may not be useful to define utility in patients in an unstable state.

As this a retrospective analysis of clinical care, there was no objective verification of medication compliance or attempt to influence the timing of intake of food or medication relative to blood drawing at the kidney/hypertension clinic: lack of standardization contributes to variability in results. However, use of fasting levels of glucose / C-Peptide may not be a resolution since relevant research from Korea and Japan have reported greater variability in fasting levels of C-Peptide than after stimulation with glucagon and intake of carbohydrate [32,33]. In our analysis, a study subject is included in the sulfonyl group due to use of that drug during the study despite a negative history on 3 or more other visits.

## 7. Conclusion

We are indebted to earlier work emphasizing an improved understanding of post prandial C-peptide levels as a guide to therapy [34–37]. Our retrospective study of 87 stable patients with type 2 diabetes demonstrated that glucose/c-peptide ratios may fall with diminished renal function. Low glucose/C-peptide ratios occur more often in geriatric patients, are associated with decreased eGFR, and likely are associated with a higher risk of hypoglycemia events. Evaluation of elevated glucose/C-peptide ratios may represent an early warning biomarker representing loss of pancreatic beta cell function. Use of insulin secretagogues in individuals over 70 years of age with both diminished renal function and glucose/C-peptide ratios may expose them to excess risk of hypoglycemia with decreased cognitive function. On the basis of our observations we consider that glucose/C-peptide levels might be useful in older patients once eGFR falls below 50 ml/min. Such observations have appeared helpful in longitudinal care of tertiary care patients with type 2 diabetes experiencing exhaustion of pancreatic function as age or disease diminish renal function over time [38]. Further studies are warranted to determine whether following glucose/C-peptide ratios may be helpful in improving healthcare outcomes.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2019.02.015>.

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