Effect of a Tight Glycemic Control Protocol on Hypoglycemia and Mortality in the Burn Unit: A Case-Control Study

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ABSTRACT: **Background:** Burn injury pathophysiology is characterized by severe catabolic state and poor glycemic control. A tight glycemic control protocol using insulin for burn victims has yielded inconsistent mortality and morbidity outcomes.

Objectives: To compare the effect of standard and tight glycemic control protocols on mortality and hypoglycemia events in critical care burn patients.

Methods: We conducted a case-control study of burn victims admitted to the burn intensive care unit between 2005 and 2011. Patients were assigned to either a standard or a tight glycemic control protocol.

Results: Of the 38 burn patients in the study, 28 were under a tight glycemic control protocol. No differences in glucose area-under-the-curve per day levels were observed between the groups (148.3 ± 16 vs. 157.8 ± 16 mg/dl in the standard and tight glycemic control protocol groups respectively, $P = 0.12$). The hypoglycemic event rate was higher in the tight glycemic control protocol group (46.4% vs. 0%, $P = 0.008$). No difference in mortality rate was noted (67.9% vs. 50%, $P = 0.31$). Mortality-independent risk factors found on multivariate analysis included total body surface area (adjusted hazard ratio [AHR] 1.039, 95% confidence interval [95%CI] 1.02–1.06, $P = 0.001$), white blood cell count on admission (AHR 1.048, 95%CI 1.01–1.09, $P = 0.02$) and surgery during hospitalization (AHR 0.348, 95%CI 0.13–0.09, $P = 0.03$).

Conclusions: The tight glycemic control protocol in burn patients was associated with higher rates of hypoglycemic events, and no association was found with improved survival in the acute setting of burn trauma care.

IMAJ 2019; 21: 35–40

KEY WORDS: burns, insulin, intensive care, hypoglycemia, mortality

A burn injury is one of the most severe forms of trauma, with long-term physical, mental and social effects [1,2]. Burn injuries require immediate specialized care by a multidisciplinary team. Although survival rates have improved substantially over the past few decades, burn injury is still associated with high mortality and long-term morbidity rates [3].

Increased glucose tolerance and insulin resistance appears in both the short- and long-term systemic response to burn injury and plays a key role in the formation of hypermetabolic and catabolic state [4]. This state is characterized by hyperdynamic circulatory response with increased body temperature, glycolysis, proteolysis, lipolysis, and futile substrate cycling, leading to loss of up to 25% of body mass [5,6]. The association between glycemic control and outcome in critically ill patients gained increased interest in recent decades. Both observational and interventional studies reported conflicting results regarding the effect of variability in glucose level on mortality in general [7-9] and on burn patients specifically [10]. Lower mortality and morbidity rates were associated with a tight glycemic control protocol in critically ill patients [11-13].

A previous study noted that 26% of patients treated with a tight glycemic control protocol suffered episodes of hypoglycemia. A possible explanation is that a glucose range of 130–150 mg/dl does not cause protein glycosylation, which occurs at glucose levels of 150–160 mg/dl and is not associated with the risk of severe hypoglycemia. A target range below 150 mg/dl would prevent protein glycosylation and be beneficial in terms of post-burn morbidity and mortality [14]. The effect of tight glycemic control on critically burn patients and its association with morbidity and mortality remain unclear.

We assumed that a tight glycemic control protocol, compared with a standard protocol, would lead to better glycemic control and reduce morbidity and mortality in severely burned patients. In the pilot study described here we compared mortality, the rate of hypoglycemia events, and adverse outcomes between burn patients under a tight glycemic control protocol and a standard protocol.

PATIENTS AND METHODS

This retrospective cohort study was conducted in the Burns Unit of Sheba Medical Center, Tel Hashomer. The participants selected for the study were taken from the registry of the Burns Unit that included all patients admitted to the unit from January 2005 to August 2011.

We enrolled to the study burn patients with total body surface area (TBSA) ≥ 20%, receiving nasogastric feeding and with a history of type II diabetes mellitus or whose blood glucose level was ≥ 140 mg/dl. Exclusion criteria were type I diabetes mellitus, or patients receiving oral nutrition in addition to nasogastric tube feeding in order to eliminate oral nutrition as a confounding variable. In the early years of the study all patients admitted to the burn unit were on a standard glycemic control protocol. This group of patients constituted the control group. In the later years of the study, all patients admitted to the burn unit were on a tight glycemic control protocol. This group of patients constituted the intervention group.

TIGHT GLYCEMIC CONTROL PROTOCOL

Glycemic control was achieved by intravenous (IV) insulin (Humulin R (Eli Lilly, Indiana, USA) or Actrapid (Novo Nordisk, UK). All forms of diabetes medication orders were terminated. Hourly capillary glucose measurements were taken. Target blood glucose levels were 131–150 mg/dl. IV insulin infusion start rate was 2, 4 or 6 units/hour for glucose levels of 121–180, 181–249, or higher than 250 mg/dl, respectively. An increment of 1 or 2 units/hour of IV insulin was given for blood glucose levels of 151–180 or above 180 mg/dl, respectively. If the insulin dose remained unchanged for three consecutive measurements, the measurement rate was reduced to every 2 hours. At a glucose level below 80 mg/dl, IV insulin was stopped and IV glucose 5% solution was given at a rate of 100 ml/hour. At a glucose level below 50 mg/dl, 20 ml of IV 20% glucose solution was given. In case of malabsorption, diarrhea or feeding discontinuation for any reason, the protocol was stopped and reactivated upon resolution.

Target blood glucose levels for patients in the control group were lower than 180 mg/dl. Blood glucose levels were measured up to 6 times daily, and corrected accordingly.

This study received Institutional Review Board (IRB) approval (# SMC-9922-12).

VARIABLES

Initial data of the eligible participants, including demographics, medical history and hospitalization, were obtained from the burn registry file and hospital computerized medical records database. Prior medical history variables included hypertension, chronic renal failure, ischemic heart disease, diabetes mellitus, chronic obstructive pulmonary disease, hyperlipidemia, and smoking. Hospitalization data obtained from the registry included TBSA, burn mechanism (fire, electrical, water, chemical, or other), inhalation injury, multi-trauma injury, measurements on arrival (blood pressure, white blood count, creatinine and blood glucose), need for intubation during hospitalization, surgery during hospitalization, Baux score, revised Baux score, protocol start day, number of days on protocol, length of stay, and mortality.

Blood glucose measurements were obtained by glucometer (Optium Xceed, Abbott Diabetes Care Inc., Alameda, CA, ISO 15197:2003) [14]. Blood glucose area under the curve (AUC) per day was calculated by the sum of consecutive glucose measurements and was used for statistical analysis.

STATISTICAL METHODS

Statistical analysis was conducted using SPSS software v.21 (SPSS technologies, IBM, USA). Continuous variables were presented as mean ± standard deviation and were compared using the independent Student *t*-test. Categorical variables are presented as counts and valid percentage. Differences in categorical variables were compared using $\chi 2$ test, or the Fisher exact test. Correlation between variables was performed using the Spearman correlation test. Multivariate analysis for mortality and hypoglycemia was performed using the Cox hazard model. Values are presented using unadjusted hazard ratio (HR) with a confidence interval (CI) of 95%. Variables that had *P* values ≤ 0.2 were included in the multivariate analysis. Analysis for cross-referencing mortality and hypoglycemia was done using the Mantel-Haenszel Model. Values are presented using odds ratio with a CI of 95%.

RESULTS

Between 2005 and 2011, 610 patients were admitted to the burn unit. Following exclusion, 10 burn patients who received standard insulin treatment were assigned to the control group, and 28 patients on a tight glycemic control protocol were assigned to the intervention group.

Baseline characteristics of both groups are presented in Table 1. The mean age of the control and intervention groups was 41 ± 10.6 and 56 ± 18.3 years ($P = 0.005$), respectively. Flame was the most common mechanism of burn in both the intervention and control groups (20/28 and 8/11 respectively, $P = 0.074$). TBSA was 50.7 ± 27% in the control group and 50.3 ± 28% in the intervention group ($P = 0.970$).

Outcome data are presented in Table 2. Hypoglycemia was documented in 13 patients (46.4%) of the intervention group compared to none (0%) in the control group ($P = 0.008$). Mean number of hyperglycemic events was 18.7 ± 29.4 in the control group versus 49.6 ± 70.3 in the intervention group ($P = 0.065$). A higher rate of hyperglycemic events was found in the intervention group than in the control group (3.2 ± 2.1 vs. 1.3 ± 0.8 events per day, $P < 0.001$). No significant differences were found in the

Table 1. Baseline characteristics

		Control (N=10)	Intervention (N=28)	*P* value
Mean age*		41.1 ± 10.59	56.18 ± 18.31	0.004
Female gender**		4 (40%)	10 (35.7%)	0.809
Hypertension**		1 (10%)	9 (32.1%)	0.172
Type 2 DM glucose › 140		10 (100%)	28 (100%)	0.087
Chronic renal failure**		0 (0%)	1 (3.6%)	0.545
Ischemic heart disease**		0 (0%)	5 (17.9%)	0.152
Dyslipidemia**		0 (0%)	2 (7.1%)	0.385
Chronic obstructive pulmonary disease**		0 (0%)	2 (7.1%)	0.385
Active smoker**		5 (50%)	11 (42.3%)	0.677
Mechanism**	Fire Electrical Water Chemical Other	8 (80%) 2 (20%) 0 (0%) 0 (0%) 0 (0%)	20 (71.4%) 0 (0%) 3 (10.7%) 2 (7.1%) 3 (10.7%)	0.074
Inhalation Injury**		7 (70%)	19 (67.9%)	0.900
Multi-trauma**		3 (30%)	4 (14.3%)	0.271
TBSA*		50.7% ± 26.92%	50.32 ± 28.18	0.970
Baux Score*		91.80 ± 29.17	106.5 ± 28.98	0.178
Revised Baux Score*		103.70 ± 31.13	118.04 ± 27.17	0.176

*Continuous variables presented as mean ± standard deviation
**Categorical variables presented as counts and valid percentage
DM = diabetes mellitus, TBSA = total body surface area

Table 2. Hospitalization data

		Control (N=10)	Intervention (N=28)	*P* value
Days hospitalized*		47.3 ± 24.51	41.68 ± 48.57	0.643
Glucose on arrival*		145.5 ± 31.29	179.04 ± 73.66	0.061
Urea on arrival*		30.4 ± 15.06	39.96 ± 22.72	0.152
Creatinine on arrival*		1.05 ± 0.38	1.29 ± 1.06	0.325
WBC on arrival (in 10^3) *		18.96 ± 16.84	16.10 ± 11.22	0.551
Blood pressure on arrival**	Normal Low High	3 (30%) 7 (70%) 0 (0%)	10 (35.7%) 14 (50%) 4 (14.3%)	0.362
Systolic blood pressure on arrival*		111.5 ± 26.16	124.36 ± 28.08	0.177
Diastolic blood pressure on arrival*		58.6 ± 18.88	68.18 ± 15.65	0.124
Surgery during hospitalization**		7 (70%)	16 (57.1%)	0.475
Protocol start day*		4.5 ± 4.8	6.8 ± 6.5	0.32
Total number of glucose measurements*		78.1 ± 75.08	183.68 ± 173.30	0.013
Time on protocol (days)*		12.75 ± 11.68	14.27 ± 13.91	0.741
Blood glucose area under the curve per day*		148.28 ± 16.07	157.78 ± 16.25	0.121
Number of glucose measurements per day*		6.33 ± 1.19	13.63 ± 3.09	0.000
Patients with hypoglycemic event**		0 (0%)	13 (46.4%)	0.008
Hyperglycemia*		18.7 ± 29.35	49.64 ± 70.33	0.065
Time to hypoglycemia (days)*		12.75 ± 11.68	10.59 ± 12	0.624
Hyperglycemia daily rate*		1.33 ± 0.84	3.21 ± 2.05	0.000
Hyperglycemia density score*		8.57 ± 15.74	8.11 ± 17.92	0.941
Positive blood culture***		9 (90%)	25 (89.3%)	0.950
Mortality**		5 (50%)	19 (67.9%)	0.315

*Continuous variables presented as mean ± standard deviation
**Categorical variables presented as counts and valid percentage
***Two or more positive blood cultures growing the same organism
WBC = white blood cells

mortality rate between both groups (5/10 vs. 19/28, $P = 0.315$).

On univariate analysis, mortality was associated with TBSA, inhalation injury, blood glucose levels on arrival, WBC on arrival, surgery during hospitalization, Baux score, revised Baux score, and number of hyperglycemic events [Table 3]. The occurrence of a hypoglycemic event during hospitalization was associated with TBSA, hyperlipidemia, blood glucose and diastolic blood pressure on arrival, Baux score, revised Baux score, and tight glycemic control protocol [Table 4]. The occurrence of a hypoglycemic event was positively associated with mortality (OR = 5.08, 95%CI 0.929–27.76, $P = 0.061$).

On multivariate analysis, independent risk factors for mortality during hospitalization were TBSA (AHR = 1.039, 95%CI 1.02–1.06, $P < 0.001$), WBC on arrival (AHR = 1.048, 1.01–1.09, $P = 0.02$), and surgery during hospitalization (AHR = 0.348, 95%CI 0.13–0.09, $P = 0.031$). An independent risk factor for hypoglycemic event during hospitalization was TBSA (AHR = 1.039, 1.02–1.06, $P < 0.001$).

DISCUSSION

Our study objective was to assess how implementation of a tight glycemic control protocol influences the occurrence of hypoglycemia, hyperglycemia, length of stay, and mortality. To our surprise, the control group had no observed events of hypoglycemia whereas 13 patients suffered hypoglycemic events in the intervention group (46.4%, $P = 0.008$). Patients in the intervention group had more than double the observed hyperglycemic events than the control group (49.64 vs. 18.7, respectively). Upon further analysis, though, it was shown that the density of events, taking into account the number of daily measurements in each group, was similar (0.25 vs. 0.21). More patients in the intervention group died during hospitalization (67.9% vs. 50%), but this was not statistically significant. Hypoglycemia was found to be associated with mortality, with an OR of 5.077 ($P = 0.061$).

During the past few decades there has been increased interest among clinicians and researchers in the association of glycemic control with morbidity and mortality of critically ill patients. Van Den Berghe et al. [15] compared the effects of tight glycemic control (glucose levels of 80–110 mg/dl) versus conventional therapy (glucose levels 180–200 mg/dl) and found that tight

Table 3. Univariate analysis for mortality

		Unadjusted HR	95%CI	*P* value
Gender		1.757	0.73–4.25	0.211
Age		0.995	0.97–1.02	0.695
Mechanism	Fire			0.728
	Electrical	1.807	0.23–14.19	0.574
	Water	0.447	0.10–2.00	0.292
	Chemical	1.646	0.37–7.33	0.513
	Other	1.226	0.28–5.43	0.788
TBSA		1.039	1.02–1.06	0.000
Inhalation injury		2.115	0.79–5.65	0.135
Multi-trauma		1.588	0.53–4.78	0.411
Hypertension		0.682	0.27–1.70	0.413
Chronic renal failure		1.628	0.21–12.52	0.639
Ischemic heart disease		0.535	0.15–1.86	0.325
Dyslipidemia		1.677	0.21–13.48	0.627
Chronic obstructive pulmonary disease		0.360	0.04–2.89	0.337
Smoker		1.223	0.51–2.92	0.651
Urea		1.002	0.98–1.02	0.834
Creatinine		1.173	0.82–1.67	0.377
Glucose on arrival		1.007	1.00–1.01	0.043
WBC		1.000	1.00–1.00	0.001
Systolic blood pressure on arrival		0.994	0.98–1.00	0.360
Diastolic blood pressure on arrival		0.989	0.97–1.01	0.326
Surgery during hospitalization		0.440	0.18–1.05	0.064
Hypoglycemia		0.999	0.41–2.45	0.998
Baux score		1.030	1.01–1.05	0.002
Revised Baux score		1.041	1.02–1.06	0.000
Blood glucose area under the curve per day		1.001	0.97–1.03	0.973
Hyperglycemia density		0.896	0.03–24.38	0.948
Hyperglycemia count		0.979	0.96–0.99	0.005
Tight glycemic control Protocol		1.186	0.43–3.26	0.741

CI = confidence interval, WBC = white blood cells, TBSA = total body surface area

Table 4. Univariate analysis for hypoglycemia

		Unadjusted HR	95%CI	*P* value
Male gender		3.286	0.87–12.40	0.079
Age		1.005	0.97–1.04	0.738
Mechanism	Fire			0.795
	Electrical	0.000	0.00–99.99	0.991
	Water	1.032	0.20–5.27	0.969
	Chemical	2.815	0.57-13.80	0.202
	Other	1.200	0.15-9.87	0.866
TBSA		1.038	1.01-1.07	0.004
Inhalation injury		0.481	0.15–1.55	0.220
Multi-trauma		0.467	0.06–3.67	0.469
Hypertension		0.900	0.26–3.15	0.870
Chronic renal failure		0.045	0.00–8798	0.618
Ischemic heart disease		1.556	0.40–6.05	0.523
Dyslipidemia		6.586	1.20–36.15	0.03
Chronic obstructive pulmonary disease		1.022	0.13–8.28	0.984
Diabetes mellitus		1.174	0.36–3.85	0.791
Smoker		1.718	0.52–5.70	0.376
Urea		1.002	0.981.02	0.870
Creatinine		0.836	0.40–1.75	0.636
Glucose on arrival		1.008	1.00–1.02	0.072
WBC		1.021	0.96–1.08	0.513
Systolic blood pressure on arrival		1.009	0.99–1.03	0.336
Diastolic blood pressure on arrival		1.032	1.00–1.07	0.073
Surgery during hospitalization		1.230	0.37–4.12	0.737
Baux score		1.036	1.01–1.06	0.003
Revised Baux score		1.035	1.01–1.06	0.006
Blood glucose area under the curve per day		1.012	0.97–1.06	0.591
Hyperglycemia density		1.272	0.02–105.2	0.915
Hyperglycemia count		0.998	0.99–1.01	0.685
Tight glycemic control protocol		36.162	0.19–6750.06	0.179

CI = confidence interval, WBC = white blood cells, TBSA = total body surface area

glycemic control reduces the rate of mortality (especially among patients in septic shock and multi-organ failure), bacteremia, acute renal failure, and need for prolonged mechanical ventilation. In contrast to those findings, the VISEP, GLUCONTROL and NICE SUGAR studies found tight glycemic control to be associated with an increased rate of hypoglycemia, and an independent risk factor for mortality (HR 3.31, 95%CI 2.23–4.90, $P = 0.001$; OR 1.91, 95%CI 1.07–3.42, $P = 0.01$; OR 1.14, 95%CI 1.02–1.28, $P = 0.02$; respectively) [7-9].

CRITICALLY ILL BURN PATIENTS AND GLYCEMIC CONTROL: ASSOCIATION WITH MORBIDITY AND MORTALITY

Pidcoke and co-workers [10] found an association between high glucose variability (percentage of measurements outside a target range of 80–110 mg/dl) and increased mortality in severely burned patients. Jeschke et al. [16] noted a decline in infection, sepsis and mortality among severely burned pediatric patients if glucose levels were below 130 mg/dl for 75% of the acute hospitalization. Aforementioned outcomes were also improved if daily average glucose was 140 mg/dl or below for 70% of the entire hospitalization. Another recent study by Jeschke et al. [17] found that patients with at least one episode of hypoglycemia had a greater inflammatory response and expressed significantly higher acute-phase proteins than those who had not experienced hypoglycemia. The study found that hypoglycemic episodes correlate with injury severity and inhalation injury. When adjusted for injury severity, hypoglycemia was associated with significantly higher post-burn morbidity and mortality [17].

A link between glucose levels and infections has also been established. Hemmila and researchers [11] found a decreased rate of infection (pneumonia, ventilator-associated pneumonia, urinary tract infection) in patients under a tight glycemic control protocol with glucose target levels of 100–140 mg/dl as compared to a control group. However, no change in mortality or length of stay was found when comparing both groups [11]. In the first-mentioned study of Jeschke et al. [16] patients under a tight glycemic control protocol (target range 80–110 mg/dl) also had a significantly decreased incidence of infections and sepsis ($P < 0.05$). Furthermore, they found that patients on a tight glycemic control protocol had significantly decreased acute-phase reactants, improved muscle protein synthesis, attenuated lean body mass loss, decreased hypermetabolism, and accelerated donor-site healing time [16]. These data are supported by other studies as well [11-13].

TBSA was found to be an independent risk factor for both mortality and hypoglycemia. WBC was found to be an independent risk factor for mortality. These findings are in accordance with previous studies [18-20].

It can be seen that by merely implementing a set protocol for glucose management in the burn unit the amount of daily measurements more than doubled. This might also explain, in part, the 'paradoxical' results regarding hyperglycemia which was found to be higher in the tight glycemic control protocol group. When very few daily measurements are taken, with many hours between each, it is possible to miss events of either hypoglycemia or hyperglycemia due simply to the fact that they are not recorded.

The higher rate of hypoglycemia in the intervention group is in accordance with other studies [7-9,16,17,21]. When insulin is given to reduce a lower glucose level, such as in the intervention group, there is greater risk of causing hypoglycemia.

STUDY LIMITATIONS

The limitations of the present study stem mainly from its relatively small sample size and possible selection bias due to its observational methodology and baseline differences between the groups (such as age). We tried to overcome this limitation by conducting a multivariate analysis in order to control for possible confounders. Inaccuracy of blood glucose measurements was also possible. It has been previously shown that both anemia and polycythemia may lead to over- or underestimation of actual blood glucose levels [22,23]. Although this might lead to underestimation of risk factors, we agreed that it is a non-differential bias that would not overturn the differences found.

CONCLUSIONS

In this study, we demonstrated how establishing an organized protocol leads to better knowledge of patients' glycemic indexes throughout the day, providing physicians with a more comprehensive viewpoint of patient care. We found no relation between the type of insulin protocol used and risk of mortality. In light of recent data aggregated since the initiation of this protocol in our burn unit, indicating a target range of 130–150 mg/dl, it might be advantageous to the prognosis of burn patients to re-examine the protocol and adjust it to said range and, in addition, attempt to keep glucose levels within this range for as long as possible throughout the day. Due to the small sample size of this study, it cannot be determined whether its current format is beneficial or advantageous. A further large-scale study is warranted.

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Capsule

Patients with systemic lupus erythematosus show an increased arterial stiffness that is predicted by IgM anti-β2-glycoprotein I and small dense high-density lipoprotein particles

Parra et al. investigated the metabolic and immunologic factors associated with the presence of central arterial stiffness as measured by the augmentation index (AIx). They conducted a cross-sectional study of 69 female patients with systemic lupus erythematosus (SLE) compared with a control group of 34 healthy women. The anthropometric variables, the vascular studies, and the analytic data were obtained the same day. The AIx was assessed by peripheral arterial tonometry. The analysis of lipoprotein populations was performed using nuclear magnetic resonance (NMR) spectroscopy. Arterial stiffness was increased in patients with SLE compared with control subjects (mean ± SD 20.30 ± 21.54% vs. 10.84 ± 11.51%, $P = 0.0021$). Values for the AIx were correlated with the Framingham risk score ($r = 0.481$, $P < 0.001$), carotid intima-media thickness ($r = 0.503$, $P < 0.001$), systolic blood pressure ($r = 0.270$, $P < 0.001$), and age ($r = 0.365$, $P < 0.001$). Patients receiving anti-malarial drugs had a lower AIx (mean ± SD 11.74 ± 11.28% vs. 24.97 ± 20.63%, $P = 0.024$). The AIx was correlated with the atherogenic lipoproteins analyzed by NMR. The immunologic variables associated with the AIx were C4 ($r = 0.259$, $P = 0.046$) and IgM anti-β2-glycoprotein I (IgM anti-β2GPI) ($r = 0.284$, $P = 0.284$). In the multivariate analysis, age (β = 0.347, 95% confidence interval [95% CI] 0.020–0.669, $P = 0.035$), IgM β2GPI (β = 0.321, 95%CI 0.024–0.618, $P = 0.035$) and small dense high-density lipoprotein (HDL) particles (β = 1.288, 95%CI 0.246–2.329, $P = 0.017$) predicted the AIx.

Arthritis Care Res (Hoboken) 2019; 71: 116

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Capsule

All-cause and cause-specific mortality in patients with granulomatosis with polyangiitis: a population-based study

Tan et al. investigated all-cause and cause-specific mortality in patients with newly diagnosed granulomatosis with polyangiitis (GPA) between two calendar time periods: 1997–2004 and 2005–2012. Using an administrative health database, the authors compared all patients with incident GPA with non-GPA controls matched for gender, age, and time of entry into the study. The study cohorts were divided into two subgroups based on the year of diagnosis: early cohort (1997–2004) and late cohort (2005–2012). The outcome was death (all-cause, cardiovascular disease [CVD]-related cancer-related, renal disease-related, and infection-related) during the follow-up period. Hazard ratios (HR) were estimated using Cox proportional hazards models, first adjusted for age, gender, and time of entry and then adjusted for selected covariates based on a purposeful selection algorithm. Included in this study were 370 patients with GPA and 370 non-GPA controls, contributing 1624.8 and 18671.3 person-years of follow-up, respectively. Sixty-eight deaths occurred in the GPA cohort, and 310 deaths occurred in the non-GPA cohort. Overall, the age-, gender-, and entry time-adjusted all-cause mortality HR in the GPA cohort was 3.12 (95% confidence interval [95%CI] 2.35–4.14). There was excess mortality due to CVD-related causes, but not cancer, in the GPA cohort. Reports of death due to infection or renal disease was not included because the numbers of death were insufficient (< 6 deaths for each outcome). All-cause mortality significantly improved between the early cohort and late cohort time periods (HR 5.61 and 2.33, respectively; P for interaction = 0.017). This population-based study showed increased all-cause and CVD-related mortality risks in patients with GPA. There was significant improvement in the all-cause mortality risk over time, but the risk remained increased compared with that in the general population.

Arthritis Care Res (Hoboken) 2019; 71: 155

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"He who has imagination without learning has wings but no feet"

Joseph Joubert (1754–1824), French moralist and essayist