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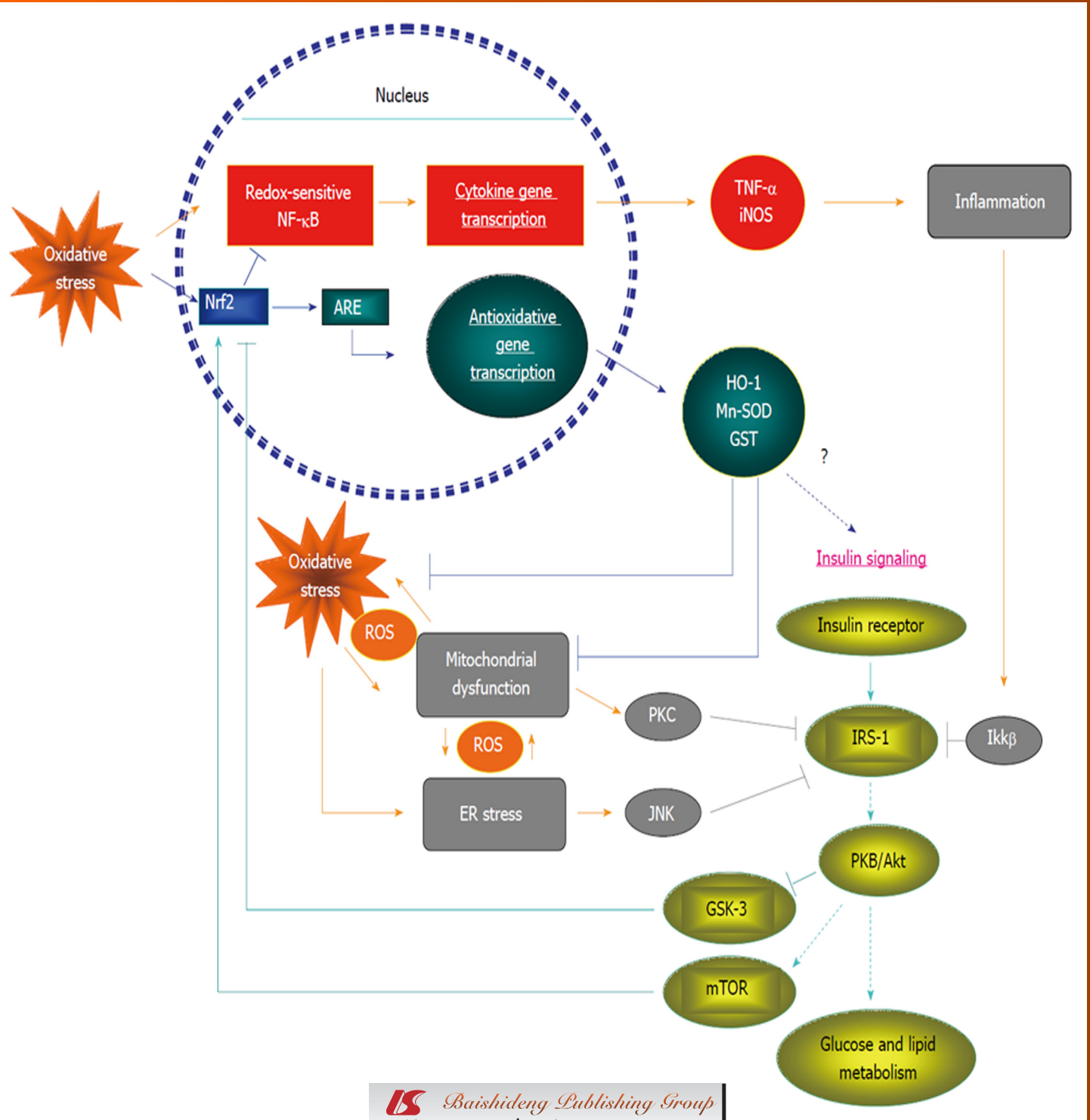

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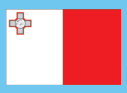

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BRIEF ARTICLE

Diabetes patients and non-diabetic patients intensive care unit and hospital mortality risks associated with sepsis

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Abstract

AIM: To compare mortality risks associated with known diabetic patients to hyperglycemic non-diabetic patients.

METHODS: PubMed data base was searched for patients with sepsis, bacteremia, mortality and diabetes. Articles that also identified new onset hyperglycemia (NOH) (fasting blood glucose > 125 mg/dL or random blood glucose > 199 mg/dL) were identified and reviewed. Nine studies were evaluated with regards to hyperglycemia and hospital mortality and five of the nine were summarized with regards to intensive care unit (ICU) mortality.

RESULTS: Historically hyperglycemia has been believed to be equally harmful in known diabetic patients and non-diabetics patients admitted to the hospital. Unexpectedly, having a history of diabetes when admitted to the hospital was associated with a reduced risk of hospital mortality. Approximately 17% of patients admitted to hospital have NOH and 24% have diabetes mellitus. Hospital mortality was significantly increased in all nine studies of patients with NOH as compared to known diabetic patients (26.7% ± 3.4% *vs* 12.5% ± 3.4%, $P < 0.05$; analysis of variance). Unadjusted ICU mortality was evaluated in five studies and was more than doubled for those patients with NOH as compared to known diabetic patients (25.3% ± 3.3% *vs* 12.8% ± 2.6%, $P < 0.05$) despite having similar blood glucose concentrations. Most importantly, having NOH was associated with an increased ICU and a 2.7-fold increase in hospital mortality when compared to hyperglycemic diabetic patients. The mortality benefit of being diabetic is unclear but may have to do with adaptation to hyperglycemia over time. Having a history of diabetes mellitus and prior episodes of hyperglycemia may provide time for the immune system to adapt to hyperglycemia and result in a reduced mortality risk. Understanding why diabetic patients have a lower than expected hospital mortality rate even with bacteremia or acute respiratory distress syndrome needs further study.

CONCLUSION: Having hyperglycemia without a history of previous diabetes mellitus is a major independent risk factor for ICU and hospital mortality.

Key words: Diabetes; Bacteremia; Sepsis; Intensive care unit mortality; Hospital mortality

Peer reviewer: Semir Ozdemir, Associate Professor, Department of Biophysics, Faculty of Medicine, Akdeniz University, Antalya 07058, Turkey

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INTRODUCTION

Small increases in fasting blood glucose concentrations (and A1c levels) have been associated with a significant risk for

cardiovascular mortality and all cause mortality[1,2]. For example, a mean fasting blood glucose of 104.5 mg/dL was associated with a 1.19 odds ratio (OR) for all cause mortality (1.05-1.35, $P < 0.05$)[1]. The OR for mortality was 1.61 (1.35-2.25) when the fasting blood glucose was 113 mg/dL (equilivent to an A1c of 6.1%). Maybe patients at risk for diabetes mellitus have an elevated hospital mortality risk when ill with new onset hyperglycemia (NOH).

Somewhat unexpectedly, mortality in critically ill patients has been reported to be significantly higher in patients without a history of diabetes mellitus compared to patients with diabetes[3-5]. The greater the blood glucose concentration in non-diabetic patients, the greater the mortality[4]. Adults with NOH, defined as a fasting blood glucose > 125 mg/dL or a random blood glucose > 199 mg/dL in non-diabetic individuals was associated with a 3-fold intensive care unit (ICU) and 5-fold increased hospital mortality rate when compared to diabetic patients[6].

Unexpectedly, bacteremic diabetic patients have a lower hospital mortality rate when compared to nondiabetic patients (24.1% *vs* 44.0%, $P < 0.05$)[7]. In addition, known diabetic patients with bacteremia are less likely to develop septic shock than non-diabetics (4% *vs* 13%, $P < 0.05$), and less well to develop acute renal failure (7% *vs* 19%, $P < 0.05$)[7]. The adjusted OR for mortality was 0.47 (0.25-0.88, $P < 0.05$) for diabetic patients when compared to non-diabetic patients with bacteremia (21.6% *vs* 37.2%, $P < 0.05$)[8]. However, not all studies have demonstrated a reduced mortality in diabetics with bacteremia. For example, one study ($n = 1112$) demonstrated a slight reduction in hospital mortality rate (8.2% *vs* 7.2%, $P = 0.39$, non-diabetics *vs* diabetics)[9]. The similar or reduced mortality in bacteremic diabetic patients was unexpected and may be secondary to the patients previous exposure to hyperglycemia (recent exposure raising the mortality risk and more chronic exposure potentially blunting the acute deleterious effects of hyperglycemia on septic mortality). Other studies have seen dramatic differences in ICU mortality rates when groups have been identified as having NOH as compared to patients with established diabetics mellitus[6,10-17].

The reason for apparently reduced mortality in hospitalized patients with diabetes mellitus is unknown. Potentially, a sudden increase in blood glucose concentration with acute illness observed in the prediabetic patient (A1c 5.5% to 6.4%) may produce dysregulation of the immune system and serious consequences of infection prevail. An alternative explanation could be related to potential benefits of traditional medication given to the diabetics as an outpatient (Statins, ACE, Aspirin, *etc.*) which may help reduce inpatient mortality. The purpose of this study was to identify if having diabetes with previous hyperglycemia or having NOH alters ICU and hospital mortality risk.

MATERIALS AND METHODS

All Pubmed references up to January 2012 were searched for all articles associated with key words of mortality and hyperglycemia. Manuscripts were excluded if they involved acute trauma, ACS, MI, CHF, CVA and pediatrics. Selection criteria required reporting three groups: (1) data meeting criteria for NOH; (2) normal glycemia; and (3) diabetes mellitus as separate groups. A few papers using the cutoff of 180 mg/dL were identified and excluded from the analysis.

Eight research papers were identified that met inclusion criteria. A ninth research paper met inclusion criteria after personal communications with the author and the author's permission to include the data provided (Person Communications March 2010)[10]. Primary endpoints were NOH (fasting blood glucose > 125 mg/dL or > 199 mg/dL twice; History of diabetes and normal glycemia. Unadjusted mortality data was obtained and compared between the three groups by analysis of variance (ANOVA). Meta analysis was obtained using the BioStat program. Figure 1 demonstrates a weighted summary log transformed statistics for the analysis of the nine studies. Data analysis was reported as mean ± SE. Significance was defined as a $P < 0.05$.

Table 1 Unadjusted intensive care unit mortality

NOH (%)	History of diabetes (%)	Hospitalized patients without NOH (%)	Ref.
31.0	11.0[a]	10.0[a]	[6]
15.2	5.2[a]	8.3[a]	[10]
10.1	5.6[a]	5.2[a]	[11]
27.4	10.6[a]	13.7[a]	[13]
43.0	31.4[a]	27.2[a]	[14]
mean ± SE 25.3 ± 3.3	12.8 ± 2.6[a]	12.9 ± 2.1[a]	

[a]$P < 0.05$ *vs* patients with new onset hyperglycemia (analysis of variance). NOH: New onset hyperglycemia.

RESULTS

Nine studies of 20 966 patients demonstrated that NOH was seen in approximately 17% (range 2%-31%) of the patients admitted to the hospital. A history of diabetes was seen in 23.9% of patients admitted to the hospital. Therefore, approximately 59% of patients were admitted without NOH or history of diabetes.

ICU mortality was evaluated in five studies (Table 1). ICU mortality was more than doubled for those patients with NOH as compared to diabetic patients (25.3% ± 3.3% *vs* 12.8% ± 2.6%, $P < 0.05$). ICU mortality was similar between diabetics and normal glycemic non-diabetics (Table 1).

Hospital mortality is summarized in Table 2. Hospital mortality was significantly increased in all nine studies of patients with NOH as compared to known diabetic patients (26.7% ± 4.4% *vs* 12.5% ± 3.4%, $P < 0.05$; ANOVA). Mortality in patients with an admission history of diabetes was similar to those patients with normal glycemia (Table 2). Meta-analysis demonstrated an increased OR for mortality in patients with NOH (OR = 2.71,

Table 2 Unadjusted hospital/intensive care unit mortality

NOH (%)	Known history of diabetes (%)	Hospitalized patients without NOH (%)	Sample size (*n*)	Patients diagnosis	Ref.
16.0	3.0[a]	1.7[a]	2030	Hospital	[6]
15.2	5.2[a,c]	8.3[a]	2713[1]	ICU	[10]
10.0	5.6[a]	5.2[a]	7285	ICU	[11]
43.8	14.8[a,c]	5.3[a]	62	Hospital	[12]
27.4	10.6[a]	13.7[a]	189	ICU	[13]
43.0	31.4[a]	27.2[a]	830	ICU	[14]
19.6	6.1[a]	3.9[a]	6367	Hospital	[15]
42.5	24.6[a]	13.7[a]	265	Hospital	[16]
23.2	11.4[a]	11.2[a]	1155	Hospital	[17]
mean ± SE 26.7 ± 4.4	12.5 ± 3.4[a]	10.0 ± 2.8[a]	20 966		

[1]Personal communications with author with permission to include and publish. [a]$P < 0.05$ *vs* patients with new onset hyperglycemia [analysis of variance (ANOVA)]; [c]$P < 0.05$ *vs* patients with normal glycemia (ANOVA). NOH: New onset hyperglycemia; ICU: Intensive care unit.

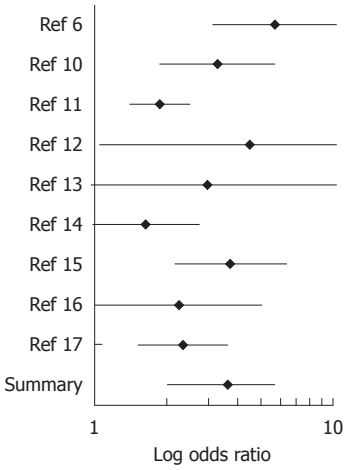

Figure 1 Mortality risk of new onset hyperglycemia *vs* diabetes mellitus. Six of the nine studies demonstrated a significant increase in mortality risk associated with new onset hyperglycemia as compared to patients with diabetes mellitus. Summary analysis demonstrated a significant increased mortality risk (odds ratio 2.7, $P < 0.05$) for new onset hyperglycemia *vs* diabetes mellitus.

95% CI: 2.03-3.61, $P < 0.001$). Figure 1 demonstrates a weighted summary statistics for the analysis of the nine studies. Using meta-analysis, a significant increase in mortality was seen for seven of the nine studies of patients with NOH compared to diabetic patients.

DISCUSSION

Having a history of diabetes prior to admission to the hospital, where the hyperglycemia is not new, may be a protective factor in that your immune system may have adapted to the hyperglycemia over time. In fact, in over 10 million patients, diabetic patients had a reduced hospital mortality when compared to non-diabetic patients OR of 0.87, 95% CI: 0.83-0.91, $P < 0.001$[5]. Unfortunately, blood glucose concentration was not reported in this study to identify if the greater mortality in the non-diabetic patients was due to some 20% of the patients with NOH and greater mortality risk.

Fortunately, a recent study has evaluated the role of hyperglycemia in non-diabetic patients. Hospital mortality was significantly increased at all mean blood glucose ranges (111-145, 146-199, 200-300 and > 300 mg/dL) in non-diabetic patients when compared to diabetic patients[4]. While these authors did not focus on admission blood glucose concentration, a similar relationship between admission blood glucose and mortality was seen by Cheung[15]. For example, OR adjusted mortality was doubled for non-diabetic patients compared to diabetic patients with an admission blood glucose between 144-179 mg/dL[15]. Unfortunately, blood glucose concentrations alone may not be a great marker of systemic injury in diabetic patients since diabetic patients have varying degrees of insulin deficiency in that a higher blood glucose observed in a diabetic patient may not reflect a greater injury but a longer duration of diabetes and less β cell function (for type 2 diabetes).

Dissecting the acuteness of hyperglycemia provides new identifiable risk factors with regards for diabetic status and NOH. The enclosed data demonstrates a protective role that hyperglycemic diabetics patients may have when they are hospitalized. Diabetic patients are less likely to develop acute respiratory distress syndrome (ARDS) than patients without diabetes[18]. Only 25% of diabetic patients with septic shock develop ARDS as compared to 47% in non-diabetic patients in septic shock. Even after adjustment of several risk factors for the development of ARDS, diabetic patient have an OR of 0.33 (90% CI: 0.12-0.90, $P < 0.05$) for the development of ARDS[18]. One explanation for this unexpected finding is that mortality may be increased in the non-diabetic group because approximately 1/5) of these patients will have NOH which may promote the inflammatory response (or prevent that anti-inflammatory response such as seen with glucocorticoid therapy).

The incidence of NOH is common in hospitalized patients and may develop from the common finding of prediabetes in the developed world population. NOH has been reported to occur in 12% of hospitalized patients[4,6] and approximately 27% of ICU patients[6,10]. We found in this review that NOH occurs in approximately 17% of

all admissions. NOH was seen in those patients that had a mildly increased A1c concentration (5.7% ± 0.3%)[16] upon admission. Mortality is higher in a non-diabetic hyperglycemic patient with an A1c > 5.4%[1]. In addition, this association suggests that mild elevation in A1c measurement (similar to what is now being call pre-diabetes) might account for a large portion of patients admitted with NOH. Furthermore, the increasing incidence of abnormal A1c levels in the world will likely contribute to a greater number of hospital admissions of non-diabetic patients with NOH.

There are several other explanations as to why diabetic patients have a reduced mortality when compared to patients without a history of diabetes who develop hyperglycemia due to injury. Many diabetic patients admitted to the hospital have recently been taking cardioprotective medications. Guidelines suggest that diabetics routinely be provided medications that impact on survival (HMG CoA reductase inhibitors, ACE, ARB, asprin and calcium channel blockers). For example, mortality is significantly reduced in bacteremic patients who had previously been treated with HMG CoA reductase inhibitor therapy[19-22]. The attributable mortality was reduced from 20% to 3% in one study[19] and hospital mortality was reduced from 23.1% to 10.6% in a second study (OR 0.39, 95% CI: 0.17-0.91, $P < 0.05$)[20]. Furthermore, if HMG CoA reductase inhibitor therapy was continued during the hospital stay, the OR for mortality was greatly reduced (0.06; 95% CI: 0.01-0.44, $P < 0.01$)[20]. Even if prior HMG CoA reductase inhibitor therapy was stopped upon admission to the hospital, a mortality benefit persisted (0.37 risk adjusted OR, $P < 0.05$)[21].

Prior ACE therapy[19] or ARB therapy[22] appear to have similar mortality benefits in users as compared to non-users. Diabetic patients undergoing renal transplant have a reduced mortality if they had been given β-blocker and calcium channel blocker medications (mean survival of 72.5 mo *vs* 36.8 mo, $P < 0.005$)[23].

An additional possibility for the observed lower mortality rate in patients with diabetes may be due to the fact that they likely receive insulin administration sooner than those with NOH. An emergency room physician may be more inclined to administer insulin sooner to a patient with a history of diabetes than non-diabetic patients. Paradoxically, critically ill non-diabetic patients provided intravenous insulin demonstrated a mortality benefit over that seen in diabetic patients[24].

Potential risk factors are many that may be contributory for specific diagnosis that may explain why one observes an increase mortality risk in hospitalized patients with NOH. Acute hyperglycemia increases risk for mortality from pneumonia in non-diabetic patients with a 30-d average blood glucose concentration above 109 mg/dL[25]. For example, the OR for mortality was 1.43 with a 30-d mean blood glucose concentration between 110-198 mg/dL, 1.65 between 199-252 mg/dL and 1.91 for a concentration greater than 252 mg/dL (all $P < 0.05$). In contrast, diabetic patients failed to have a significant increase in mortality (OR of 0.96; NS) with a blood glucose between 110 mg/dL and 198 mg/dL. Consistent with the diabetic protective effect, the OR was also not significant for diabetic patients with regards to mortality risk even with a mean blood glucose concentration between 199 mg/dL and 252 mg/dL (OR of 1.24; NS). This appears counter-intuitive but acuteness of the hyperglycemia (within a few days or weeks) may play a pivotal role in septic mortality risk. Unfortunately the mechanism is not known.

In this group of community acquired pneumonia patients, mortality was only increased in diabetic patients with the highest blood glucose, an average blood glucose > 252 mg/dL (OR = 1.43, $P < 0.05$). The higher glucose threshold for an increase in mortality risk seen in established diabetic patients suggest that they their body's immune system may adapt to hyperglycemia over time. Consistent with this is the fact that bacteremia and fungemia are much more common in patients with NOH. The OR was 4.2-fold increased (1.5-12, $P < 0.05$) for development of bacteremia or fungemia in chemotherapy patients who also had acute hyperglycemia[26]. While none of the bacteremia studies use the criteria for the diagnosis of NOH, mortality was increased 3-fold in patients with a blood glucose > 170 mg/dL compared to patients with a lower blood glucose concentration[27]. This suggests that acute elevations in blood glucose concentration below the 199 mg/dL cutoff for the criteria of NOH may also carry additional mortality risk.

Increased mortality may also be related to cardiac function during illness. For example, the electrical conduction pathway is altered by acute hyperglycemia that may not be seen in diabetic patients who have many hyperglycemic episodes. Acute hyperglycemia prolongs both QT interval and QTc dispersion in diabetic patients and in acute hyperglycemic patients. However, the prolonged QTc dispersion does not rapidly recover in acute hyperglycemia. QTc dispersion recovers normally in diabetic patients[28]. An alternative hypothesis worth testing is to see if an increased QTc dispersion may contribute to mortality risk seen in those patients with NOH due to illness (infection, sepsis, *etc.*).

Lastly, coronary artery plaque instability may be a reason for increased mortality risk. One earlier study showed that normal volunteers had acute hyperglycemia which blunted the optimal response to injury by reducing MMP-3 concentration and altering plaque stability[29]. Elevated blood glucose concentration may contribute to coronary and carotid plaque rupture. While cytokine levels (tumor necrosis factor-α, IL-6) are similar in both diabetic and non-diabetic septic patients, there is a significant reduction in anticoagulants seen in non-diabetic patients[14]. The lower concentrations of Protein S and Antithrombin may contribute to an alteration in the normal coagulation profile and promote coronary plaque unstability.

In summary, in someone who is hyperglycemic, having a history of diabetes mellitus appears to lower one's

risk for hospital and ICU mortality. The exact mechanism behind this is unknown but may likely be due to the body's ability to adapt to hyperglycemia over an extended period of time. In comparison, developing NOH in adults increased the OR for mortality by 2.7-fold. Since recent clinical trials of intravenous insulin treatment have failed to confirm a mortality benefit in all ICU patients[24,30], and it may even show harm[30], studies to test the benefits in a more select group of patients seems warranted.

Recent recommendations have increased target blood glucose goals in hospitalized patients due to the lack of evidence associated with aggressive insulin treatment. Unfortunately, none of the earlier studies have evaluated the benefit of intravenous insulin treatment in patients with NOH)[30]. The median blood glucose for treated patients was 144 mg/dL)[30]. Since the mortality risk is increase 2.7-fold greater in patients with NOH as compared to diabetic patients it would seem rational to test the benefits of early aggressive insulin treatment in this select group of non-diabetic patients. Furthermore, it would seem equally important to identify risk factors for those who are at risk to develop NOH. Some of these risk factors include: family history of diabetes, metabolic syndrome, impaired fasting glucose or an A1c concentration consistent with the diagnosis of pre-diabetes (5.5%-6.4%). As of 2012, the ADA recomends an A1c measurement as part of the admission labs to hospital. Septic patients in the ER with NOH have recently been shown to have 2.1 fold OR for mortality as compared to known diabetics with similar blood glucose concentration[31]. Identifying NOH will identify patients with a high mortality risk.

COMMENTS

Background

Diabetes is known to increase the risk for multiple infections with serious infections a common reason for hospital admission. Some patients without diabetes when they become ill also have elevated blood glucose concentrations due to illness that are similar to the concentration seen in patients with diabetes. For example, a random blood glucose above 199 mg/dL is not uncommon in hospitalized patients with and without diabetes. The elevated blood glucose in the non-diabetic patient is likely due to the patient having prediabetes. Prediabetes is defined as someone having a fasting blood glucose between 100 mg/dL and 125 mg/dL. Approximately 20% of the US population is considered to have pre-diabetes. It is possible that a large proportion of pre-diabetic patients who are hospitalized develop an elevated blood glucose concentration above 199 mg/dL. The novel and acute elevated in blood concentration likely reduces the persons' immune response to fight infection which would explain the 2.7-fold observed increase in mortality as compared to diabetic patients with a similar blood glucose concentration.

Research frontiers

Understanding the immunological reason for the greater mortality in patients with new onset hyperglycemia (NOH) is paramount. While it is well known that neutorphill phagocytosis is reduced at elevated blood glucose concentrations other critical immune functions may be reduced with acute hyperglycemia. Research to identify those factors is needed.

Innovations and breakthroughs

The breakthrough has begun with the use of this knowledge to help identify seven additional studies that have demonstrated a higher mortality risk in patients with NOH as compared to patients with known diabetic mellitus. Using this information in the emergency room or after surgery may identify patients at very high mortality risk as compared to patients without an elevated blood glucose concentration.

Applications

This study established the criteria for the diagnosis of NOH which will become an important marker of hospital mortality risk. In addition, it will help direct new research into testing benefits of treatment of hyperglycemia in non-diabetic patients. An ICD9 code should be established for the diagnosis of NOH.

Terminology

NOH is defined as two fasting blood glucose concentrations greater than 125 mg/dL or two non-fasting glucose concentrations above 199 mg/dL or one of each. This criteria, while used on an out patient bases for the diagnosis of diabetes mellitus, does not make the diagnosis of diabetes mellitus in the inpatients setting due to the fact that illness is known to increase blood glucose concentrations due to an increase in the stress hormones (cortisol, GH, Catacholamines, Glucagon). The reason why the blood glucose increases greater than 199 mg/dL with illness is likely due to the patient have pre-diabetes.

Peer review

This is a good descriptive in which the authors analyze the association between blood glucose concentration and whether the patient has had a history of hyperglycemia in the past or NOH. Historically, blood glucose concentrations were perceived to be of equal risk when seen in a hospitalized patient. These authors support the hypothesis that NOH has a very high mortality risk as compared to hyperglycemia that may be more chronic as seen in many diabetic patients. The results of the study demonstrate that all the research trials have demonstrated a similar trend and that seven of the nine trials have a significant increase in hospital or intensive care unit mortality was observed in patients with NOH.

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Toddlers' choice: Yo-Yoing diabetes control or deci-unit insulin dosing?

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Abstract

While the incidence of toddlers' diabetes is soaring, their mainstay insulins were withdrawn, namely the weak 10% or 20% insulin mixtures (WIM), which were injected only once or twice daily. Consequently, toddlers are coerced to use an insulin pump, multi-dose insulin regime (MuDIR), mix or dilute insulins. This paper highlights the difficulties and proposes a simple solution. While an insulin pump is the best available option, it is not readily available for everyone. Mixing insulins is not sufficiently precise in small doses. Although diluting insulin would allow precise dosing and reduce the dose variability secondary to dribbling after injections, it, like insulin mixing, deprives children from using the pen and related child-friendly accessories. In MuDIR, we inject 4-5 small doses of insulin instead of 1-2 daily larger doses of WIM. Thus, on using a half unit (½ unit) insulin pen, a dose of 0.5, 1, 1.5 and 2 units are adjusted in steps of 100%, 50%, 33% or 25%; unlike the advisable 5%-20%. This does not easily match the tiny erratic meals of grazing toddlers. Maternal anxiety peaks on watching yo-yoing glycemia. Carers have to accept either persistently high sugar or wild fluctuation. The risks of such poor glycemic pattern are increasingly recognized. Using insulin U20 in a ½unit disposable pen allows deci-unit dosing, with 5%-20% dose-tuning, greater accuracy on delivering small doses and reduction of dose variability from dribbling. Deci-unit dosing may help avoid wide glycemic swings and provide the affordable alternative to insulin pumps for toddlers. Deci-unit pen materializes the Human Rights of Children, a safer and effective treatment.

Key words: Child; Toddler; Diabetes; Insulin pen; Insulin mixture; Insulin dribbling; Deci-unit dosing; Deci-unit pen, Insulin U20; Glycemic control

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TO THE EDITOR

Over the past few decades, standardization of insulin preparations to 100 unit/mL (U100) significantly reduced dosing errors. Insulin U20 was withdrawn with little resistance from pediatric diabetologists[1,2]. Recently, as the incidence of diabetes is soaring worldwide, especially in toddlers, and we became more aware of its complications, toddler-friendly insulin mixtures were discontinued[3,4]. The vulnerable youngsters are left fighting the merciless diabetes with inappropriate [mixing insulins,

multiple dose insulin regimes (MuDIR)], cumbersome (diluting insulins) or unaffordable (insulin pump) therapeutic alternatives.

Toddler-friendly insulins were 10% or 20% rapid-intermediate weak insulin mixtures (WIM) that were injected once or twice daily. Doses were adjusted in coarse (15%-20%) or fine (5%-10%) tuning, for steady control. Withdrawal of WIM forced the use of insulin pumps, free insulin mixing or MuDIR.

Free insulin mixing is not a popular option anymore. Recently, diluting U100 insulin to U10 has been successfully studied[5]. This should prove to be a major boon to young diabetic patients and their families[6]. However, mixing or dilution necessitates the use of insulin syringes. The more accurate modern insulin delivery devices, pens, Microfine®, PenMate® and Autocover®, have redefined parents expectations[4]. Now, mixing is rarely acceptable since it is not as accurate or reliable as pens[7]. Mixing and diluting insulin share the inconvenience of carrying the unsightly syringes and needles around, especially on holidays. The highly technical insulin pump is not widely available, particularly in developing countries or at the outset, as it demands complex multidisciplinary care and resources, which are scarce.

Using multiple 5-20 μL insulin doses is inaccurate[8]. As pens deliver insulin in half unit (½unit) steps, dose tuning becomes impractical (Figure 1), let alone dribbling of the concentrated insulin, U100. For instance, if a dose of ½unit proves insufficient, the next dose is one unit, a 100% increment. One wonders: (1) Would an adult diabetologist advise fine tuning a dose from 5 units to 10 units in one step? (2) Why should a mother accept dose adjusting from ½unit to 1 unit? Or stay at ½unit to avoid "hypos"?

We propose using deci-unit dosing, i.e., using U20 in ½unit disposable pens, which is compared with ½unit dosing in Figure 1. At low doses, 5 units or less, adjustment could be best achieved by the proposed "0.1 unit dose tuning" rather than by "0.5 unit dose jumping". The latter force mothers to keep a smaller dose longer and blood sugar higher to avoid "hypos" until the child grows.

With ½unit dosing, only as doses creep up to 3 units does coarse tuning become feasible but fine tuning is unavailable until doses exceed 5 units. Frequently, parents and professionals have to choose between a high "yo-yoing" control and persistently high glycemia. Annersten *et al*[9] reported significant insulin dribbling from needles [on average 4.7 mg (approximately 0.5 units) in NovoPen3] after 7 s; therefore, they recommended needle holding in the skin for 10 s to minimize dose loss. This practice might add fuel to the fire in a discontent child. Is this avoidable?

We studied the ½unit pens, new HumaPen Luxura HD® (HPL) and NovoPen Junior® (NPJ), by counting the number of drops that get through the tip of 5 mm/31G Microfine needles on slow pressing of the push button in each of the doses 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4.0, 4.5, 5.0, 10.0 units. Three pens of each type were tested and the experiment for each dose was repeated 10 times so that the number of drops in each dose is averaged from data of 30 experiments for each pen. The HPL dribbled a mean of 0.24 (SD = 0.21) units/drop and the NPJ dribbled 0.33 (0.32) (unpublished data). After insulin injection, a drop or rarely two might dribble from the needle tip. Losing one drop is sizable and variable; it constituted 63%, 30%, 20%, 15%, 12% and 10% of the doses 0.5, 1, 1.5, 2, 2.5 and 3 units, respectively.

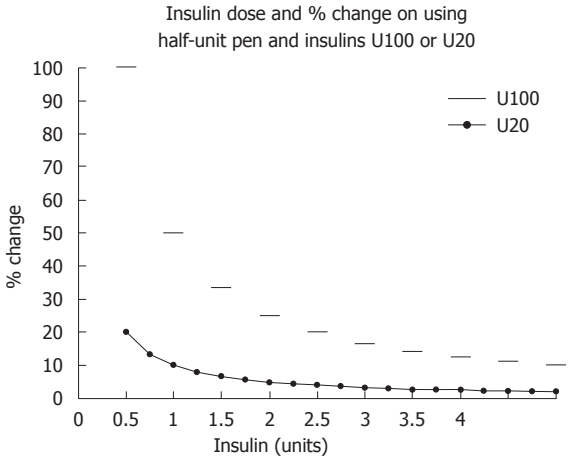

Figure 1 Percent changes in dosing on using ½unit pen with U100 and U20 insulins. (−−) Abrupt ½unit dosing (U100 current practice): Dose "jumping" is the only way for doses < 3 U. Dose coarse-tuning is available if doses > 3 U, fine-tuning in doses 5 U; (-•-) Smooth deci-unit dosing (U20 proposed alternative).

Certainly, this highly variable insulin loss with dribbling further complicates diabetes care. Logically, insulin dribbling from U20 insulin would be only one fifth of the standard U100, raising hopes of reducing the 10 s injection hold-in time in needle-phobes.

Assuming no WIM return, the proposed alternative would be rapid insulin of U20. Using U20 in ½unit pen ensures deci-unit dosing and fine tuning. To avoid dispensing errors, the deci-unit pen should be disposable and only prescribed on a named patient basis. Thus, toddlers would continue benefiting from the ever-improving quality convenient pens and their child-friendly accessories.

Surely, there exists a compassionate insulin manufacturer who would love to cater for diabetic youngsters, however small the market is. The disposable deci-unit pen will allow a wider range of safer dosing and deci-unit tuning that is expected to improve accuracy on delivering small insulin doses. It, like diluting insulin, may also reduce insulin loss from dribbling which might ease-up injections due to a shorter holding-in time, besides allowing the continuing use of pens, the affordable alternative to insulin pumps for poor and developing nations.

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Events Calendar 2012

January 15-17, 2012
ICADIT 2012: International conference on Advances in Diabetes and Insulin Therapy
Zurich, Switzerland

January 29-February 3, 2012
Genetic and Molecular Basis of Obesity and Body Weight Regulation
Santa Fe, NM, United States

February 3, 2012
The Future of Obesity Treatment
London, United Kingdom

February 8-11, 2012
5th International Conference on Advanced Technologies and Treatments for Diabetes
Barcelona, Spain

February 9-10, 2012
EC Conference on Diabetes and Obesity Research - Save the Date
Brussels, Belgium

February 21, 2012
Association of Children's Diabetes Clinicians 6th Annual Meeting
Coventry, United Kingdom

February 23, 2012
Diabetes and kidney disease: advances and controversies
Birmingham, United Kingdom

March 1-3, 2012
International conference on Nutrition and Growth
Paris, France

March 7-9, 2012
Diabetes UK Annual Professional Conference 2012
Glasgow, United Kingdom

March 15 -16, 2012
Monogenic Disorders of Insulin Secretion: Congenital Hyperinsulinism and Neonatal Diabetes
Philadelphia, PA, United States

March 15 -17, 2012
2012 DF Con - Diabetic Foot Global Conference
Hollywood, CA, United States

March 19-22, 2012
Society for Endocrinology BES 2012
Harrogate, United Kingdom

March 22-25, 2012
2nd Latin America Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Rio de Janeiro, Brazil

March 29-31, 2012
The 4th International Conference on Advances in Diabetes and Insulin Therapy
Riga, Latvia

March 29-April 1, 2012
New Frontiers in Diabetes Management
Ocho Rios, Jamaica

April 2-6, 2012
6th Annual Primary Care Spring Conference: Session 1
Palm Coast, FL, United States

April 4-7, 2012
39th Panhellenic Congress of Endocrinology and Metabolism
Athens, Greece

April 11-13, 2012
ICDM 2012: International Conference on Diabetes and Metabolism
Venice, Italy

April 11-13, 2012
ICDHLSP 2012: International Conference on Diabetes, Hypertension, Lipids and Stroke Prevention
Venice, Italy

April 16-17, 2012
Paediatric and Adolescent Diabetes
Birmingham, United Kingdom

April 22-25, 2012
9th International Podocyte Conference
Miami, FL, United States

May 9-12, 2012
19th European Congress on Obesity
Lyon, France

May 23-27, 2012
AACE 21st Annual Scientific and Clinical Congress - American Association of Clinical Endocrinologists
Philadelphia, PA, United States

May 24-27, 2012
27th Annual Clinical Conference on Diabetes
Bonita Springs, FL, United States

June 8-12, 2012
American Diabetes Association's 72nd Scientific Sessions
Philadelphia, PA, United States

June 29-August 2, 2012
ESE Summer School on Endocrinology
Bregenz, Austria

August 1-4, 2012
AADE 39th Annual Meeting - American Association of Diabetes Educators
Indianapolis, IN, United States

September 13-16, 2012
EMBO-EMBL Symposium: Diabetes and Obesity
Heidelberg, Germany

October 1-5, 2012
48th European Association for the Study of Diabetes Annual Meeting
Berlin, Germany

November 7-9, 2012
40th Meeting of the British Society for Paediatric Endocrinology and Diabetes
Leeds, United Kingdom

November 8-11, 2012
The 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Barcelona, Spain

December 4-6, 2012
1st American Diabetes Association Middle East Congress
Dubai, United Arab Emirates

World Journal of Diabetes

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INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

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The columns in the issues of *WJD* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in diabetes; (9) Brief Article: To briefly report the novel and innovative findings in diabetes research; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJD*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of diabetes mellitus; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in diabetes mellitus.

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Title: Title should be less than 12 words.

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There are unstructured abstracts (no less than 256 words) and structured abstracts (no less than 480). The specific requirements for structured abstracts are as follows:

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Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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For articles of these sections, original articles, rapid communication and case reports, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1948-9358/g_info_20100107165233.htm.

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Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

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Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$.

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Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

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Format

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1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 200201 03498. 2002 Aug 1

Statistical data
Write as mean ± SD or mean ± SE.

Statistical expression
Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units
Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1948-9358/g_info_20100107145507.htm.

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Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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