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Insulin Units and Conversion Factors: A Story of Truth, Boots, and Faster Half-Truths

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Abstract

Conventional insulin concentration units (IU/mL or just U/mL) are bioefficacy based, whereas the Système International (SI) units (pmol/L) are mass based. In converting between these two different approaches, there are at least 2 well-accepted conversion factors, where there should be only 1. The correct value is not the most-used or well-accepted using online calculators, some journal styles, laboratory reports, and published articles. In short, an incorrect insulin conversion factor is widely used which underreports insulin concentrations by ~15%, with potentially significant research and clinical implications. This short commentary describes the history of insulin IU definitions and conversion factors, and highlights the widespread nature of conversion factor misuse, to provoke deeper interest and thought regarding numbers we so often use without thinking.

Keywords

insulin, insulin history, insulin potency, insulin standards, insulin unit conversion, international units

The Problem

In converting human insulin from conventional (units, ml) to SI units (pmol, l), there are 2 (maybe even 3) conversion factors, but only 1 is right. It is not the one most used in online conversion calculators and tables, and it is not necessarily the one recommended in some journal's style guides. This issue is open to widespread use of incorrect values in research, analysis, and care.

The Actual Problem

The conventional units (international units, IU or just U) for insulin are based on bioefficacy, rather than the mass/count-based units of the Système International (SI) units. Since its discovery in 1922, the definition of the amount of insulin required to achieve a standard glycemic effect has changed several times. The different conversion factors between conventional and SI units can essentially be traced back to differences in standards and purity of insulin preparations. The issue of real concern is the conversion factor most visible in literature and online conversion tools is based off old and superseded standards, and imprecise measurements of the atomic weight of insulin.

This issue has been noted several times over the past couple of decades,[1-4] seemingly without wide uptake in practice. This area of confusion has important clinical and research implications, as insulin concentrations may be ~15% in error if the incorrect conversion factor is used.[2,5] Indeed, this is the reason the issue came to our attention, as we had reference concentrations that were low in IU/mL, which didn't make sense.

The correct conversion factor between conventional and SI units for human insulin is 1 μIU/mL = 6.00 pmol/L.

History, or How This Came About

The history of the insulin Unit has been well reviewed elsewhere,[6,7] but it is, in short, a history of change. Originally defined as the amount of insulin required to cause convulsive hypoglycemia in a fasted 2kg rabbit,[6] standards for potency (IU per mg or equivalent) have changed with improvements in the preparation and stabilization of insulin in solution. Where potency was defined in the 1920s as 8 IU/mg of insulin,[6] this definition was revised upward in 1959 by the World Health Organization (WHO) Expert Committee on Biological Standardization's Fourth International Standard to 24 IU/mg.[8] It was revised upward

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Table 1. Summary of Key Insulin Potency Standards and Calculation of Associated Unit Conversion Factors.

		Potency			Conversion factor $1\frac{\mu IU}{mL} = [\,]\frac{pmol}{L}$
	Molar mass (g/mol)	(IU/mg)	(mg/IU)	(nmol/IU)	
Fourth International Standard (1959)	5808	24	0.01417		7.174
NIBSC code: 83/500 (1986)	Impure insulin	26	0.0385	6.0[a]	6.622[a]
	5808	28.8	0.0347	6.0	6.00
Common (incorrect) conversion factor	6000	24	0.01417		6.944

[a]These numbers differ as the 1986 standard contains some water and salts.

Table 2. Survey of Human Insulin Conventional to SI Unit Conversion Factors in Online Calculators or Tables of Units.

Insulin unit converter	Area of application	Conversion factor: $1\frac{\mu IU}{mL} = [\,]\frac{pmol}{L}$
http://www.endmemo.com/medical/unitconvert/Insulin.php	Multidisciplinary	6.945
http://unitslab.com/node/124	Laboratory/medical	6.944
http://www.scymed.com/en/smnxtm/tmbbfcc1.htm	Clinical/analytics/medicine	7.18
http://www.amamanualofstyle.com/page/si-conversion-calculator	Journal manual of style	6.945
https://www.thebloodcode.com/calculators/	Selected risk factors	6.945
http://www.globalrph.com/conv_si.htm	Clinical reference	6.945

All websites were accessed August 24, 2018.

again by the same committee in the 1986 to 26 IU/mg.[9,10] This value remains the standard to date, with the latest updates made in 2010.[11]

However, as the 1986 standard contains some water and salts, amino acid analysis gives a corrected potency of 6 nmol per 1 IU.[1,12] If instead, anhydrous insulin is considered, the 6 nmol per 1 IU potency is equivalent to 28.8 IU/mg, or 0.0347 mg/IU. This latter potency is more common and has been referred to as the established standard.[13]

As a result, there is one standard, but two human insulin potencies due to improvements in the quality of insulin preparation. The conversion factors arising from these different potencies are given in Table 1. The conversion factor resulting from the Fourth International Standard was calculated as per,[1] and can still be occasionally found (see Table 2).

However, the most visible and potentially most widely used unit conversion factor for human insulin is that 1 μIU/mL = 6.945 pmol/L. Per Table 1, this conversion seems to be an artifact calculated from an assumed molar mass of 6000 g/mol (human insulin is 5808 g/mol) and the 24 IU/mg of the WHO Fourth International Standard from 1959.[14] It is a conversion factor based on imprecise (or generously rounded) atomic mass and outdated standards, and as such should not be used in research or clinical practice.

Widespread (Mis)use

The two most commonly reported conversion factors between conventional and SI units for human insulin are 1 μIU/mL = 6.945 pmol/L (incorrect) and 1 μIU/mL = 6.00 pmol/L (correct).

Online Calculators

Many, if not all, readily accessible online insulin unit conversion calculators rely on incorrect conversion factors, as shown in Table 2. For the first 10 results in a Google search for "insulin unit conversion pmol/L mU/mL," 6 results returned either an online conversion calculator (5) or a table of references for unit conversions (1). The remaining results were either some of the articles (referenced above) querying insulin units, or question threads asking about unit conversions. It can be seen from the results in Table 2 that not one of the most visible online unit converters used the correct conversion factor.

Journal Articles

The use of conversion factors in published research is more difficult to ascertain, as many articles do not self-report unit conversion factors, particularly if unit conversions, like common acronyms, are assumed common knowledge within the area of publication. However, as an indicator, a Google Scholar search was carried out for "'insulin' '6.945'" for results from July 2017 to July 2018. Of the 37 results returned, 19 were manually filtered out as not reporting any insulin conversion factor, not returning a journal article, or not being in English. The journal publications of the remaining 18 results are shown in Table 3. Accepted results could include a

Table 3. Journals Where at Least One Article Self-Reported an Incorrect Insulin Unit Conversion (*or an Incorrect Conversion Factor was Used in a Formula) as found in a Google Scholar Search From the Period of July 2017 to July 2018.

Journal	Country of publication	Area
*Nature Genetics**	UK	Genetics
*Diabetes Care**	US	Endocrinology, diabetes and metabolism/internal medicine/advanced and specialized nursing
*Diabetologia**	Germany	Internal medicine/endocrinology diabetes and metabolism
JCEM	US	Biochemistry/biochemistry (medical)/clinical biochemistry/ endocrinology/endocrinology diabetes and metabolism/medicine (misc)
Mayo Clinic Proceedings	US	Medicine (misc)
Atherosclerosis	Netherlands	Cardiology and cardiovascular medicine
Obesity	US	Endocrinology/endocrinology diabetes and metabolism/medicine (misc)/nutrition and dietetics
Nutrition Journal (BMC)	UK	Medicine (misc)/nutrition and dietetics
Journal of Endocrinological Investigation	US	Endocrinology/endocrinology diabetes and metabolism
Journal of the Academy of Nutrition and Dietetics	US	Medicine (misc)/nutrition and dietetics/food science
Journal of Cardiovascular Pharmacology and Therapeutics	US	Cardiology and cardiovascular medicine/pharmacology/pharmacology (medical)
Journal of Clinical Biochemistry and Nutrition	Japan	Medicine (misc)
*Early Human Development**	Netherlands	Obstetrics and gynecology/pediatrics, perinatology and child health
Journal of Cosmetic Dermatology	UK	Dermatology
*Archives of Physiology and Biochemistry: The Journal of Metabolic Diseases**	Netherlands	Medicine (misc)
Journal of Clinical and Translational Endocrinology	Netherlands	Endocrinology diabetes and metabolism

Journals are ordered by impact factor, and key areas are given based on https://www.scimagojr.com (accessed August 24, 2018).

direct report of insulin unit conversion in the methods or a table (13/18), or an indirect use of the incorrect insulin conversion factor in a formula (5/18). It should be noted that the authors do not consider the results in Table 3 to comment on the quality of any of the journals noted, the intention is simply to illustrate the widespread nature of the issue.

The results in Table 3 show incorrect insulin unit conversion is a problem across continents and a wide range of journal types. In fairness, journals where an article simply referenced the incorrect conversion factor in a formula are denoted with an asterisk. Interestingly, of the 17 different journals in Table 3, 6 (35%) were quartile 1 or 2 of journals in the areas of "endocrinology" or "endocrinology diabetes and metabolism," and 7 were in quartile 1 or 2 of journals in the areas of "medicine" or "medicine (misc)." These results suggest incorrect insulin unit conversions are widespread in endocrinology and medical research, as well as in other fields who might rely on online calculators for unit conversions outside their area of expertise.

The extent of this issue is hard to ascertain without comprehensive review of journal articles reporting insulin concentration results. Many journals specify the use of SI units—for example *Diabetes* and *Diabetes Care*, which come under the umbrella of the American Diabetes Association. Few journals specify conversion factors for insulin concentrations. However the American Diabetes Association has published the conversion factor of 1 μIU/mL = 6.0 pmol/L in its table of conventional to SI unit conversions.[15] It can be seen in Table 2 that the AMA manual of style, which partners with the JAMA Network and the Oxford University Press, gives the incorrect unit conversion factor as of the time of this writing. In short, the use of incorrect insulin conversion factors seems to be a widespread issue, affecting all levels and qualities of research.

Insulin Analogues

The discussion of insulin conversion factors presented here is limited to human insulin. The WHO international standards were originally developed for human insulin, not its analogues, which differ in molecular structure (and mass) and bioactivity.[4,12,16-18] However, the potency of analogues is generally defined relative to human insulin in terms of the glycemic drop or area under the glucose curve.[4,19] Some common insulin analogues include insulin lispro (Humalog®), insulin aspart (Novorapid®), insulin glulisine (Apidra®), and insulin glargine (Lantus®), all of which have a defined potency of 1 μIU/mL = 6.00 pmol/L,[4] while insulin detemir (Levemir®) has a lower potency at 1 μIU/mL = 24.0 pmol/L.[4]

Because of differences in insulin action, the question has been raised as to whether units of insulin analogues are truly comparable.[4,20] Another critical issue in this regard is that insulin assays do not always measure, or fully measure, insulin analogues.[4] Further discussion of the measurement and

potency of insulin analogues is outside the scope of this commentary. However, caution is recommended when interpreting laboratory results for insulin analogues for these reasons.

Recommendations

For authors:

- If possible, report insulin concentrations in units of pmol/L.
- Where results are in IU/mL, or these units are pertinent to the audience, use the correct unit conversion for human insulin of 1 μIU/mL = 6.00 pmol/L, and report it in the methods.

For journals:

- In addition to specifying whether SI or conventional units are used, specify the insulin unit conversion factor to be used.

For laboratories:

- Report insulin concentrations in units of pmol/L.
- Standard laboratory report forms for insulin results should include the insulin unit conversion factor of 1 μIU/mL = 6.00 pmol/L.

Abbreviations

IU, International Units; SI, Système International; U, bioefficacy units; WHO, World Health Organization.

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