Different normalization methods, very different normal upper limit

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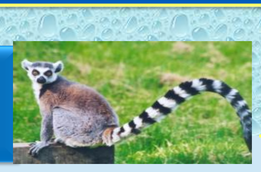
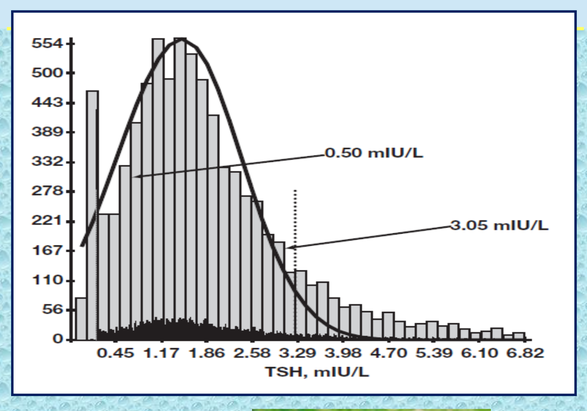
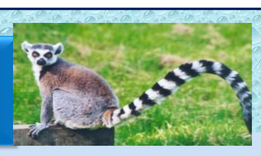
BACKGROUND



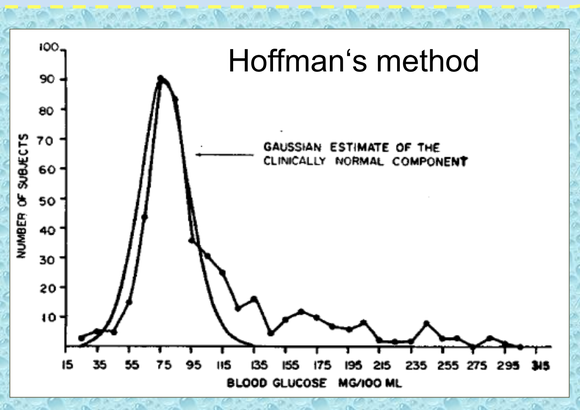
Distribution of thyroid stimulating hormone (TSH) levels is not normal (a right tail) . This is due to physiological changes that cause temporary increases in TSH during physiological events. Several methods are used to normalize the distribution when defining normal limits.



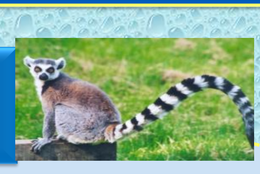
OBJECTIVE



To compare the normal limits defined by three normalization methods versus non-normalized distribution based on a large cohort with no known thyroid disease.



METHODS



Data were collected from a computerized data base of the Clalit health services, Jerusalem, Israel. Exclusion criteria were: positive anti-thyroid antibodies, treatment with any drug.

TSH values were normalized with : 1. Hoffman method - this removes the upper and lower 25 percentiles and then extrapolates the upper (97.5th percentile) and lower (2.5th percent le) normal limits. 2. Tukey's method - calculates the "inter quartile range" (IQR) as the difference between the 75th and 25th percentiles, removes the 25th percentile minus 1.5 X IQR and the 75th percentile plus 1.5X IQR and extrapolates 2.5th and 97.5th percentiles. 3. Tukey followed by natural log transformation - transforms the Tukey data by natural log transformation and then calculates the 2.5th and 97.5th percentiles.

The clinical relevance of the limits was tested by calculating the mean FT3 and mean FT4 for results of TSH below, within and above the limits for each method.

RESULTS

We report the results of the 6-10 age group, based on 1450 subjects, as a representative example. According to the non-normalized, Hoffman, Tukey and Tukey followed by NLT, the limits were 0.98-6.87, 0.95-4.31, 0.97-5.55 and 0.97-5.55 IU/l respectively, i.e. maximal change from non-normalized data occurred for the UNL by the Hoffman method (-33%) and for the LNL also by the Hoffman method (+4%). There was no difference in average FT4 between patients with TSH within, below or above the normal range for all 4 methods.

The UNL and LNL according the Tukey followed by NLT methods were almost identical to NLT alone.

6-10 Y.O – 1450 children

	TSH (mIU/L)		Average FT3 (pmol/L)			Average FT4 (pmol/L)			Average TSH (mIU/L)		
Calculation Method	Lower limit	Upper limit	TSH below LNL	TSH within limits	TSH above UNL	TSH below LNL	TSH within limits	TSH above UNL	below LNL	within limits	above UNL
non-normalized 2.5% and 97.5%	0.98 (100)*	6.87 (100)*	5.90	6.41	6.61	16.54	16.87	16.66	0.77	2.86	8.61
Hoffman	0.95 (94.5)*	4.31 (62.5)*	5.80	6.38	6.58	16.32	16.90	16.68	0.75	2.46	5.79
Tukey	0.97 (100)*	5.55 (80.5)*	5.81	6.40	6.62	16.30	16.87	16.77	0.75	2.71	7.09

Numbers in brackets – represent the percent of non-normalized 2.5/97.5 % limits•

CONCLUSIONS

1. As expected, normalization methods alter mainly the upper normal limit but the difference between methods is more than 30%.

2. In individuals without thyroid illness, thyroid hormone values are stable over a wide range of TSH levels thus questioning the value of TSH as a screening test