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Fatty acids, triglyceride structure, and lipid metabolism

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Fat structure, composition, and configuration can influence cholesterolemia and atherosclerosis. Most studies of experimental atherosclerosis involve feeding fat and cholesterol to susceptible animal species, and the cholesterolemic properties of the individual fats are accentuated by the presence of the sterol. However, experiments using cholesterol-free diets give data that are similar with regard to the effects of fats but considerably less extreme vis-à-vis cholesterolemia. Examples of the effects of unsaturation, steric configuration, and triglyceride structure are discussed. (J. Nutr. Biochem. 6:172–178, 1995.)

Unsaturated and saturated fats

Anitschkow and colleagues[1,2] in 1913 were able to induce atherosclerosis in rabbits by feeding cholesterol suspended in sunflower seed oil. For several decades thereafter workers in atherosclerosis considered the fat vehicle used for addition of cholesterol to the diet as a number of interchangeable entities. In the 1950s, the level of dietary fat was perceived as the governing factor in human cholesterolemia. Keys et al.[3] demonstrated a strong relationship between the percentage of dietary fat and cholesterolemia in a number of populations. However data were already accumulating to show that the type of fat (saturated or unsaturated) played an important role in human or animal cholesterolemia. Kritchevsky et al.[4,5] showed that a diet containing cholesterol plus an unsaturated fat was less atherogenic for rabbits than one containing a more saturated one. (*Table 1*). In 1958, Groen[6] reviewed the studies of fat and its relation to cholesterolemia and cited early studies that showed the different cholesterolemic effects of saturated and unsaturated fats. In 1957, Ahrens et al.[7] fed human volunteers formula diets containing 40% fat and showed that as the iodine value of the fat decreased (toward greater saturation) the subjects plasma cholesterol levels rose. The iodine value is a measure of the degree of unsaturation of a fat and is a reflection of the amount of iodine needed to saturate the double bonds.

In 1965, Keys[8] and Hegsted[9] and their colleagues developed formulas to predict cholesterol levels that might be observed when dietary fat was changed. The Keys formula was:

$$\Delta C = 1.35\ (2\Delta S - \Delta P) + 1.5\ \Delta Z$$

where ΔC represents the change in cholesterol level, S and P represent saturated and unsaturated fatty acids, respectively, and Z is the square root of mg of dietary cholesterol per 1000 Kcal. The Hegsted formula[10] was:

$$\Delta C = 2.16\ \Delta S - 1.65\ \Delta P + 0.168\ \Delta C\ (\text{mg/1000 kcal}) + 0.85$$

(C represents mg of dietary cholesterol). In both instances stearic acid did not give the predicted response and it was concluded that this fatty acid had no effect on cholesterol levels in humans.

To digress briefly, there is no clear-cut demarkation between saturated and unsaturated fat. Coconut oil, a fat containing 91% saturated fatty acids, still contains 7% monounsaturated and 2% polyunsaturated fatty acids. Safflower oil, a fat rich in polyunsaturated fatty acids, contains 9% saturated fatty acids. Reiser et al.[11] compared the plasma lipid responses to coconut oil, beef fat, and safflower oil in 19 young men fed meals containing 35 en% of one of the test fats. The responses to beef fat corresponded to the responses to safflower oil and both led to plasma cholesterol levels lower than those observed in subjects fed coconut oil. They concluded that grouping beef fat with coconut oil in the saturated fat category was unwarranted. The issue begs resolution.

Connor et al.[12] compared the effects of cocoa butter and corn oil in six subjects given formula diets containing 40 en% of fat. Cholesterol levels fell significantly when the subjects changed from their usual diets to the cocoa butter–rich diet. Levels of cholesterol fell further when the subjects were given the corn oil formula. In a study comparing the effects of dietary palmitic or stearic acids, Grande et al.[13] concluded, ". . . cocoa butter, a fat rich in stearic acid,

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Table 1 Influence of saturated and unsaturated fat on atherosclerosis in rabbits*

	Vehicle	
	Shortening	Corn oil
Iodine value	72	130
Serum cholesterol (mmol/L)	103.4	81.8
Average atherosclerosis†	3.17	2.17

*After Kritchevsky et al.[4]
Rabbits (14/group) fed 3% cholesterol in 9% fat for 60 days.
†Graded on a 0–4 scale.

lacks the cholesterol-raising effect expected from its total content of long chain fatty acids."

Cocoa butter (34% stearic acid) is more poorly absorbed than corn oil or palm kernel oil.[14,15] In rabbits fed a cholesterol-rich diet, cocoa butter was 24% more atherogenic than corn oil and 17% less atherogenic than either coconut oil or palm oil.[16] When rabbits were fed a cholesterol-free, semipurified atherogenic diet, cocoa butter was 253% more atherogenic than corn oil, 59% less atherogenic than palm kernel oil, and 67% less atherogenic than coconut oil.[17] Levels of serum cholesterol were (mM/L): coconut oil, 12.25, palm kernel oil, 11.27; cocoa butter, 5.68; and corn oil, 1.65. The percentage of HDL-cholesterol was: corn oil, 37.8; cocoa butter, 2.51; palm kernel oil, 8.6; and coconut oil, 7.0. Mean increases in serum cholesterol (mM/L) in rhesus monkeys fed 2% cholesterol and 25% fat for 30 days were: corn oil, 6.43; peanut oil 8.89; cocoa butter, 9.56; butter oil, 11.68; and coconut oil, 12.43.[18]

Mattson and Grundy[19,20] demonstrated that monounsaturated fat is as effective as saturated fat in lowering cholesterol levels in man. Ng et al.[21] showed that dietary oleic and palmitic acids have similar effects on serum lipids and lipoproteins in normocholesterolemic subjects (*Table 2*). Sundram et al.[22] fed male volunteers whole food diets in which 5% of energy supplied by palmitic acid was replaced by lauric plus myristic acids with all other fatty acids being kept constant. The diets contained 30% of energy as fat and supplied 200 mg/day of cholesterol. Compared with the lauric-myristic diet, the palmitic acid diet lowered total serum cholesterol by 9% and lowered LDL-cholesterol by 11%. Wood et al.[23] fed diets containing butter, crude or refined palm oil, margarine, refined palm oil–sunflower oil 4:1, and refined sunflower oil to 29 healthy middle aged men. Baseline cholesterol was 5.07 ± 0.80 mmol/L and it fell to 4.84 ± 0.72 mmol/L on sunflower oil. The average for the other five diets was 5.12 ± 0.03 mmol/L (*Table 3*).

Hayes and his coworkers[24–26] studied the effects of fats blended to five desired ratios of specific fatty acids on cholesterol metabolism in monkeys and hamsters and concluded that linoleic acid is hypocholesterolemic until it reaches 5 to 6% of calories and then has no further effect; myristic acid is hypercholesterolemic at any level of intake, and palmitic acid is hypercholesterolemic only when ingested with 400 mg or more of cholesterol per day or in subjects whose cholesterol levels exceed 5.82 mmol/L. These and other studies have given rise to expanded formulas for predicting dietary effects on cholesterol levels. Hayes' predictive formula for man on cholesterol-free diets is[27]:

$$\text{Cholesterol} = 229 + 8E_{14:0} - 36E_{18:2}$$

where E represents the energy contribution of specific fatty acids. Derr et al.[28] have offered the following, which also addresses specific fatty acids:

$$\Delta C = 2.3\Delta 14{:}0 + 3.0\Delta 16{:}0 - 0.8\Delta 18{:}0 - 1.0\ \text{PUFA}$$

where PUFA stands for polyunsaturated fatty acids.

Table 2 Comparison of palmitic and oleic acids effects in normocholesterolemic subjects*

	Value at entry	Dietary oil		
		Coconut	Palm	Olive
Plasma cholesterol (mmol/L)				
Men (n = 20)	5.02 ± 0.67	6.05 ± 0.93^{ab}	5.04 ± 0.67^{a}	5.09 ± 0.83^{b}
Women (n = 13)	4.94 ± 0.78	5.87 ± 1.22^{ab}	4.86 ± 0.70^{a}	4.86 ± 0.78^{b}
LDL cholesterol (mmol/L)				
Men	3.52 ± 0.59	4.27 ± 0.98^{ab}	3.44 ± 0.65^{a}	3.47 ± 0.80^{b}
Women	3.36 ± 0.75	4.09 ± 1.16^{ab}	3.23 ± 0.70^{a}	3.28 ± 0.78^{b}
HDL cholesterol (mmol/L)				
Men	0.93 ± 0.21	1.03 ± 0.23^{ab}	0.96 ± 0.21^{a}	0.96 ± 0.18^{b}
Women	1.19 ± 0.18	1.32 ± 0.21^{a}	1.19 ± 0.18^{a}	1.19 ± 0.21
LDL/HDL				
Men	3.91 ± 1.08	4.32 ± 1.43^{ab}	3.74 ± 1.09^{a}	3.71 ± 1.23^{b}
Women	2.89 ± 0.82	3.25 ± 1.25^{ab}	2.80 ± 0.94^{a}	2.82 ± 0.99^{b}
Plasma triglycerides (mmol/L)				
Men	1.21 ± 0.73	1.62 ± 0.90^{ab}	1.41 ± 0.91^{a}	1.42 ± 0.67^{b}
Women	0.81 ± 0.42	1.02 ± 0.34^{a}	0.94 ± 0.46	0.86 ± 0.42^{a}

*After Ng et al.[21]
Subjects were fed coconut oil diet for 4 weeks then palm or olive oil diets for 6 weeks. All diets contained 23 en% test fats (2/3rds of daily fat intake). Values in horizontal row bearing same letter are significantly ($p < 0.05$) different.

Table 3 *Influence of dietary fats on serum lipids in normocholesterolemic men**

Fat	Serum lipids (mmol/L)†			
	TC	HDL-C	LDL-C	TG
Baseline	5.07 ± 0.80	1.03 ± 0.18	3.39 ± 0.70	1.40 ± 0.63
Butter	5.17 ± 0.88	1.03 ± 0.18	3.52 ± 0.80	1.39 ± 0.71
Crude palm oil	5.15 ± 0.90	1.03 ± 0.21	3.36 ± 0.88	1.61 ± 0.91
Margarine	4.99 ± 0.72	1.00 ± 0.21	3.36 ± 0.65	1.40 ± 0.61
Refined palm oil (RPO)	5.15 ± 0.80	1.06 ± 0.23	3.41 ± 0.83	1.54 ± 0.88
RPO/sunflower 4:1	5.12 ± 0.85	1.03 ± 0.21	3.41 ± 0.83	1.44 ± 0.77
Sunflower	4.84 ± 0.72	1.00 ± 0.18	3.23 ± 0.65	1.33 ± 0.46

*After Wood et al.[23]
†TC, Total cholesterol; HDL-C, HDL-cholesterol, LDL-C, LDL-cholesterol; TG, triglycerides.
Five groups of 6 men each rotated through a 6-week diet period followed by a 6-week wash out. Diets contained 40 en% fat of which 60% was the test fat.

Mensink and Katan[29] conducted a meta-analysis of 27 controlled studies relating to changes in plasma lipids as affected by changes in carbohydrate or fatty acid intake. They concluded that the replacement of saturated by polyunsaturated fatty acids raised HDL/LDL cholesterol ratio. Hegsted et al.[30] reviewed 420 dietary observations from 141 groups of subjects and concluded that saturated fatty acids are the primary determinants of serum cholesterol, polyunsaturates lower serum cholesterol, monounsaturates have no independent effect, and dietary cholesterol increases serum cholesterol. The question does not appear to have been resolved.

Trans unsaturated fatty acids

The term "*trans* fat" refers to fats containing unsaturated fatty acids containing double bonds in the *trans* configuration. The effects of *trans* fats were reviewed a few years ago[31] but a few new questions have arisen. *Trans* fats occur in nature—in plants and in animal tissues but the principal source of *trans* fat in the human diet is hydrogenated fat. Hydrogenated fats are present mainly in margarines but also occur in salad oils, shortening, and cooking oils. In the course of hydrogenation, double bonds of fatty acids tend to migrate, and margarine may contain fatty acids with double bonds (*cis* and *trans*) between positions 4 and 16.

Trans fatty acids are metabolized like their *cis* counterparts. Carboxyl labeled oleic and elaidic acids are decarboxylated at the same rate.[32] Uniformly labeled (with ^{14}C) oleic and elaidic acids were catabolized to $^{14}CO_2$ at rates of 70 and 65%, respectively.[33] Pigs fed *cis* or *trans* fat carry them in all lipoprotein fractions.[34] Rats fed partially hydrogenated soybean oil show the presence of *cis* and *trans* fatty acids in triglycerides and phospholipids of all tissues.[35] Rats[36] or monkeys[37] fed *trans* fat accumulate *trans* unsaturated fatty acids in liver and blood but these acids disappear soon after the dietary stimulus has been removed.

Trans fats are incorporated into the membrane lipids of rat erythrocytes and liver mitochondria.[38] *Trans* fats may affect enzymes of lipid metabolism and inhibit fatty acid desaturase-elongase activity[39] as well as LCAT activity.[36] But effects on the latter may depend on dietary levels of the *trans* fat[37] (*Table 4*). Cholesteryl esters of *trans* fatty acids are synthesized[40] and hydrolyzed[41] more slowly than those

Table 4 Serum and liver enzyme levels of vervet monkeys fed *trans* unsaturated fatty acids*

Group†	Enzymes				
		Serum[a]		Liver[b]	
	LCAT	LPL-6	LPL-12	CBS-OAC	CBS-MVA
3T	52.4 ± 7.3	6.0 ± 1.1	5.9 ± 1.2	8.6 ± 1.5	17.4 ± 7.8
3R	64.8 ± 4.9	8.3 ± 1.6	12.2 ± 1.6	7.0 ± 1.0	87.3 ± 42.6
6T	73.4 ± 4.9	7.9 ± 1.3	7.5 ± 1.1	9.3 ± 1.5	19.2 ± 14.3
6R	57.7 ± 9.9	6.6 ± 1.2	6.5 ± 1.1	15.2 ± 7.0	117.3 ± 56.6
Control	59.0 ± 5.7	12.0 ± 0.9	7.5 ± 0.8	7.7 ± 0.8	81.2 ± 48.5

*After Kritchevsky et al.[37]
†3T, 8 monkeys fed 3.2% trans fat (TF) for 12 months. 3R, 8 monkeys fed 3.3% TF for 6 months returned to control diet for 6 months. 6T, 8 monkeys fed 6.0% TF for 12 months. 6R, 7 monkeys fed 6.0% TF for 6 months returned to control diet for 6 months. Control, 15 monkeys fed control diet for 12 months.
[a]LCAT, lecithin-cholesterol acyl transferase, mM/hr. LPL, lipoprotein lipase, mmol free fatty acid/ml/hr.
[b]CBS-OAC, cholesterol biosynthesis from sodium [1–^{14}C]acetate, dpm/mg P. CBS-MVA, cholesterol biosynthesis from [2–^{14}C]mevalonate, dpm/mg P.

Table 5 Liver enzyme activities in livers of rabbits fed 3.2 or 6.0% *trans* fatty acid for 5 months

Enzymes	Group (7/group)		
	3.2% *trans*	6.0% *trans*	Control
Microsomal			
Glucose-6-phosphatase (U/mg/P)	3.3 ± 0.4	2.7 ± 0.2	2.5 ± 0.4
Cytosolic			
Fatty acid synthase (mU/mg/P)	3.6 ± 0.2	3.6 ± 0.2	3.4 ± 0.3
Mitochondrial			
Malate dehydrogenase (U/mg/P)	1.4 ± 0.2	1.1 ± 0.1	1.0 ± 0.1
β Hydroxy butyrate dehydrogenase (μU/mg/P)	10.6 ± 3.7	6.7 ± 2.8	4.3 ± 2.4
Monamine oxidase (μU/mg/P)	11.6 ± 1.0	8.7 ± 0.5	10.2 ± 1.4

*After Ruttenberg et al.[42]
U, μmol of product/min means + SEM.

of *cis* fatty acids. *Trans* fatty acids do not seem to affect activity of enzymes not involved in lipid metabolism. Activities of liver microsomal, mitochondrial, and cytosolic enzymes of rabbits fed 3.2 or 6.0% *trans* fatty acids were no different from controls[42] (*Table 5*).

When rabbits were fed cholesterol plus *trans* fatty acids, serum cholesterol levels were raised significantly, but the severity of atherosclerosis was not.[43–45] Similar results were obtained in monkeys[42] or rabbits[37] fed cholesterol-free semipurified diets. Elson et al.[46] fed swine diets containing 17% fat in which the level of *trans* fat varied from 0 to 48%. After 10 months there was no effect of *trans* fat on plasma cholesterol levels, and aortic sudanophilia was observed in 5 of 64 pigs. Affected pigs came from groups fed 0, 24.8, or 48% *trans* fat.

The levels of *trans* fatty acids in tissues of subjects who have died of coronary disease and controls are similar.[47,48] Two recent reports from Netherlands[49] and Australia[50] have aroused concern that dietary *trans* fats may elevate plasma levels of Lp (a) in man. However, this phenomenon has not been observed in three different studies carried out in the USA.[51–53] The reason for the discrepancy remains to be elucidated; possibly specific *trans* fatty acids are the culprits. This aspect of *trans* fat metabolism remains to be studied.

Triglyceride structure

The structure of naturally occurring triglycerides is genetically determined. Small[54] has summarized the composition of the major triglycerides in a number of oils and fats. These are unique to each fat and differ among fats. For example, the three major triglycerides of corn oil are trilinolein, 1,3 dilinoleoyl 2 olein, and 1,2 dilinolineoyl 3 palmitin, while the major ones of both soybean and safflower oils are trilinolein, 1,2 dilinolineyl 3-olein, and 1,2 dilinoleyl 3 palmitin (*Table 6*). When fat is digested, the fatty acid in the SN2 position is conserved to about 75% in the triglyceride present in lymph.[55] Tristearin is virtually unabsorbed, but the stearic acid of mixed triglycerides is fairly well absorbed.[56]

After Hegsted had adduced different cholesterolemic roles for specific fatty acids, he proceeded to obtain specially prepared fats designed to contain an excess of one or another fatty acid.[57] The special fats were prepared by interesterification of natural fats with trilaurin, trimyristin, tripalmitin, or hydrogenated soybean oil (85% stearic acid) in a ratio of 3:1. The prepared fats contained an excess of the desired fatty acid but since they had been interesterified they had been randomized so that each component fatty acid was present in each position of the triglyceride to one-third of its total concentration. The new fats did not give the

Table 6 Major triglycerides of some natural fats and oils*

Fat or oil	Major Triglycerides†		
Butter	PPB	PPC	POP
Lard	SPO	OPL	OPO
Tallow	POO	POP	POS
Cocoa butter	POS	SOS	SOP
Corn oil	LLL	LOL	LLP
Cotton seed oil	PLL	POL	LLL
Olive oil	OOO	OOP	OLO
Palm oil	POP	POO	POL
Peanut oil	OOL	POL	OLL
Soybean oil	LLL	LLO	LLP
Safflower oil	LLL	LLO	LLP
Sunflower oil	LLL	OLL	LOO

*After Small.[54]
B, butyric; C, capric; P, palmitic; S, stearic; L, lauric.

Table 7 Effect of fat added to diets by randomization into corn oil on experimental atherosclerosis in rabbits*

Diet (No.)†	Serum cholesterol (mmol/L)	Atherosclerosis (0–4 scale)	
		Aortic arch	Thoracic aorta
Corn oil (43/46)	68.10	1.65	1.10
Randomized corn oil (42/46)	52.30	1.59	1.08
Lauric acid (19%) (41/46)	51.80	1.98	1.15
Myristic acid (18.2%) (34/46)	48.70	1.82	1.24
Palmitic acid (30%) (42/46)	53.80	2.07	1.30
Stearic acid (23.4%) (40/46)	51.40	1.74	1.08

*After Kritchevsky and Tepper.[58]
†Diet contained 2% cholesterol and 6% fat; fed for 8 weeks.

Table 8 Effects of different fats on plasma lipids in pigs*

Fat†	% 16:0	% 16:0 at SN 2	Total cholesterol (mmol/L)	LDL + VLDLC / HDLC
MCT	4.3	0.4	1.91 ± 0.10	0.50
Coconut oil	6.5	1.3	2.07 ± 0.11	0.40
Palm oil	27.0	4.4	2.17 ± 0.11	0.48
Synthetic fat	29.6	69.9	2.56 ± 0.18	0.45
Sow milk	30.7	55.3	4.47 ± 0.26	1.45

*After Innis et al.[63]
Piglets fed formula (603 kcal/L of fat) days 1–17.

anticipated changes in plasma lipids and the authors concluded, ". . . in addition to the known effects related to both chain length and saturation, the position of a fatty acid on the glyceride molecule also influences its metabolism." A study in cholesterol-fed rabbits in which corn oil was randomized with trilaurin, trimyristin, tripalmitin, or tristearin also showed no specific fatty acid effects on either cholesterolemia or atherosclerosis[58] (*Table 7*). Zock et al.[59] compared the effects of myristic, oleic, and palmitic acids on serum lipid and lipoprotein levels of men and women. One fat was prepared by interesterification of myristic, stearic, and linoleic acids with glycerol; one by blending palm, cottonseed and hydrogenated sunflower oils; and one by mixing several sunflower oils, palm oil, and an interesterified mixture of two sunflower oils. Only the palmitic acid–rich fat was in its natural structural state. The cholesterol levels (mmol/L) for all 59 probands were: myristic acid 5.19 ± 0.90; palmitic acid, 4.96 ± 0.85 and oleic acid, 4.53 ± 0.81. However, randomization of one of the test fats may have compromised the findings. Similarly, Denke and Grundy[60] compared the effects in men of high-oleic sunflower oil, palm oil, and an oil high in lauric acid prepared by interesterification of the high-oleic sunflower oil and trilaurin. They reported that the total serum cholesterol levels were 4.44 ± 0.54 mmol/L in men fed the high oleic acid fat, 4.94 ± 0.75 mmol/L in men fed the high lauric acid fat, and 5.17 ± 0.65 mmol/L in those fed palm oil. The triglyceride structure of the high lauric oil was not what one might expect to find in nature.

The positional distribution of fatty acids of human milk or infant formula influences their absorption.[61] Fat absorption was linearly related to the amount of palmitic acid in the SN2 position. Corandomization of coconut oil and palm olein increases the amount of palmitic acid in the SN2 position and renders the fat more absorbable in rats than a simple mixture of two fats.[62] Innis et al.[63] have shown recently that plasma cholesterol levels in piglets fed various fats increase as the amount of palmitic acid in the SN2 position increases. Piglets fed for 17 days on palm oil (27% palmitic acid at SN2), sow's milk (30.7% palmitic acid at SN2), or a synthetic fat (29.6% palmitic acid at SN2) exhibited plasma cholesterol levels (mmol/L) of 2.17 ± 0.10, 2.56 ± 0.18, and 4.47 ± 0.26, respectively. The synthetic fat was prepared by interesterifying a tripalmitin-rich palm oil fraction with a mixture of sunflower and canola oils (*Table 8*).

Peanut oil is a relatively unsaturated fat that is surprisingly atherogenic for rats,[64] rabbits,[65] and monkeys.[66,67] The atherogenic effect in rabbits is seen in diets containing[63] or devoid[68] of cholesterol. Randomization of peanut oil reduces its atherogenicity by 37% (*Table 9*). Randomization of lard reduces its atherogenicity by 10% in rabbits fed 2% cholesterol.[69] Randomized butter has been shown to reduce serum cholesterol in man by 11%.[70]

The foregoing show that fat structure and composition can influence cholesterolemia and atherosclerosis. Attention must be paid to both these aspects in studies involving fat effects in health and disease.

Table 9 Effect of randomization on peanut oil atherogenicity for rabbits* (average of 3 experiments)

Number	Dietary fat: Peanut oil (27/31)	R-peanut oil (31/31)	Corn oil (28/31)
Cholesterol			
Serum (mmol/L)	48.5 ± 5.07	47.5 ± 7.37	43.5 ± 5.72
Liver (g/100 g)	2.73 ± 0.27	2.43 ± 0.31	2.99 ± 0.28
Atherosclerosis			
Aortic Arch	2.22 ± 0.15^{ab}	1.31 ± 0.12^{a}	1.32 ± 0.13^{b}
Thoracic Aorta	1.54 ± 0.14^{ab}	1.05 ± 0.10^{a}	1.02 ± 0.10^{b}

*After Kritchevsky et al.[67]
Rabbits fed 2% cholesterol and 6% fat for 2 months.
R, peanut oil = randomized peanut oil.
Values in horizontal line bearing same letter are significantly ($p < 0.05$) different.

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